21 July 2011
EMA/CHMP/455587/2011
Committee for Medicinal Products for Human Use (CHMP)

CHMP variation assessment report

Type II variation EMEA/H/C/000644/II/0057 P46 052

Invented name/name:	Tygacil
International non-proprietary name/common name:	tigecycline
Indication summary (as last approved):	Treatment of: - complicated skin and soft tissue infections, excluding diabetic foot infections - complicated intra-abdominal infections Tygacil should be used only in situations where it is known or suspected that other alternatives are not suitable
Marketing authorisation holder:	Wyeth Europa Ltd

1. Scope of the variation and changes to the dossier

Scope of the variation:	Update of Summary of Product Characteristics To update sections 4.2, 4.8 and 5.2 of the Tygacil SmPC with paediatric PK and safety information based on the results of paediatric studies 3074K4-2207-WW and 3074A1-110-US, both submitted and assessed in previous procedures. This variation was requested by the CHMP on 20 January 2011.
Rapporteur:	Arantxa Sancho-Lopez
Product presentations affected:	See Annex A to the Opinion
Dossier modules/sections affected:	Modules 1 and 2

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Product Information affected:	Summary of Product Characteristics (Attachment 1 - changes highlighted)

2. Steps taken for the assessment

Step	Step date
Submission date:	7 April 2011
Start of procedure:	24 April 2011
Rapporteur's preliminary assessment report circulated on:	6 June 2011
Rapporteur's final assessment report circulated on:	20 June 2011
Request for supplementary information and extension of timetable adopted by the CHMP on:	23 June 2011
MAH's responses submitted to the CHMP on:	29 June 2011
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	11 July 2011
Rapporteur's updated assessment report on the MAH's responses circulated on:	18 July 2011
CHMP Opinion	21 July 2011

3. Scientific discussion

3.1. 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 April 2006 and is currently approved for the following indications:

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

• 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.

The Marketing Authorisation was renewed by the European Commission on 6 May 2011 following a positive CHMP Opinion of 17 February 2011. As a consequence of the benefit-risk assessment the indications have been restricted by adding the following wording in section 4.1 of the Tygacil SmPC:

"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)."

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

This type II variation application initially aimed to update section 5.2 of the Summary of Product Characteristics (SmPC) with PK information for Tygacil in the paediatric population following a request from CHMP of 20 January 2011. The PK information to be added originated from the completed paediatric studies 3074K4-2207-WW and 3074A1-110-US, both previously submitted and assessed. (study 2207 was submitted to the EMA in April 2010, in accordance with Article 46 of Regulation (EC) No. 1901/2006, study 3074A1-110-US was provided in the FU2 052.1.)

However, in its Request for Supplementary Information adopted on 23 June 2011, CHMP requested the MAH to also update sections 4.2 and 4.8 of the Tygacil SmPC with safety information in the paediatric population originating from the same two paediatric studies mentioned above.

This variation was classified as follows:

Variation requested		**Type**
C.I.4	Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

3.2. Clinical aspects

The MAH conducted and completed two pharmacokinetic studies with tigecycline in the paediatric population: study 3074A1-110-US (study 110) and study 3074K4-2207-WW (study 2207).

Study 3074A1-110-US was an open label, single, ascending dose study conducted in children aged 8-16 years and aiming to characterize the pharmacokinetics and safety/tolerability of single intravenous doses (0.5 mg/kg, 1 mg/kg and 2 mg/kg) of tigecycline. The Clinical Study Report (CSR-53874) containing the study results was provided and assessed with the responses to the first Request for Supplementary Information to the P46 052 procedure (FU2 056.1). At the time when the Paediatric Investigation Plan for tigecycline was agreed with the PDCO, this study was already completed.

The primary objective of the study was to determine the safety and tolerability of single doses of tigecycline administered as an IV infusion to children. The secondary objective was to determine the PK of single ascending doses of tigecycline in children. Each subject participated in the study for up to 6 days, including a 3-day screening period, followed by a minimum 12-hour inpatient period and a 2-day follow-up period.

50 subjects were planned to be enrolled in the study; 25 subjects were enrolled, and 24 subjects completed the study and were included in the analysis. Six dose groups were planned, but the study was stopped (as per study protocol) after 2 subjects in the 1 mg/kg dose group (ages 8 to 11 years) vomited. The final dose group planned (2 mg/kg dose in subjects ages 8 to 11 years) was omitted, and the remainder of the 1 mg/kg dose group (ages 8 to 11 years) did not complete the study.

For more details on the study design and its results please refer to the Rapporteur assessment report of procedure P46 052 from 5 July 2010 (Attachment 5).

A summary of PK parameter data by dose group and age group is shown in the table below.

Table -1: Single-Dose Tigecycline Pharmacokinetic Parameters in Children (Mean±SD)

Dose Group	**Age Group (y) [n]**	**C_{max} (mg/L)**	**AUC (mg•h/L)**	**$T_{1/2}$ (h)**	**CL (L/h/kg)**	**V_{ss} (L/kg)**

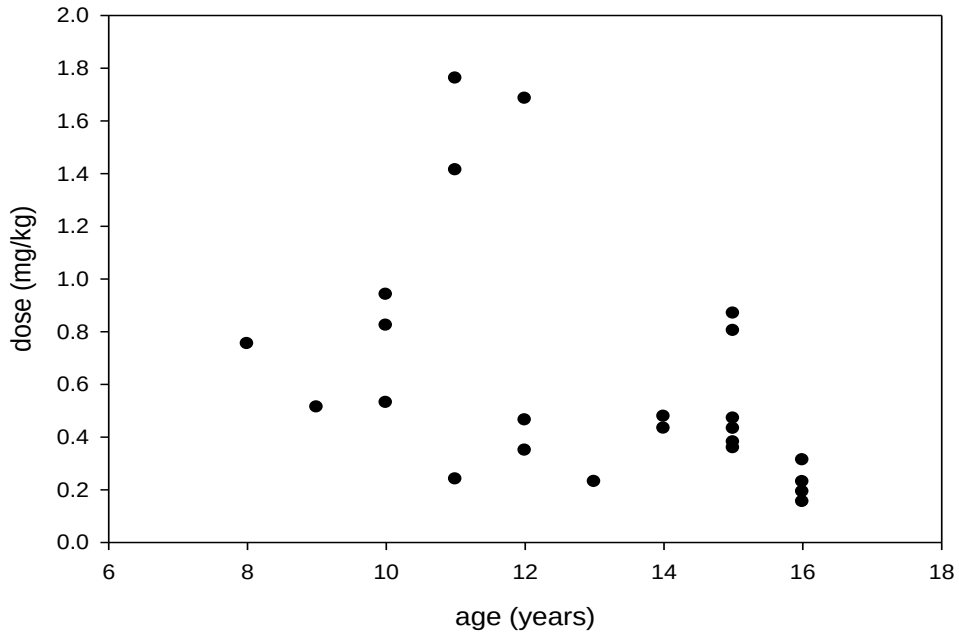
0.5 mg/kg	8 – 11 [6]	2.49±3.74	2.43±1.45	18.5±4.9	0.25±0.10	4.48±1.78
0.5 mg/kg	12 – 16 [2]	2.18±1.18	3.36±1.09	24.7±8.8	0.16±0.04	3.48±2.04
1 mg/kg	8 – 11 [2]	0.56±0.17	1.59±0.25	11.0±0.8	0.64±0.10	9.18±0.87
1 mg/kg	12 – 16 [6]	10.7±7.31	8.47±2.92	21.2±3.1	0.13±0.04	2.02±1.01
2 mg/kg	12 – 16 [4]	23.6±44.3	12.1±14.2	17.9±3.3	0.35±0.25	7.47±4.95
100 mg	Adult [224]	1.45±0.32	5.19±1.86	27.1±14.3	0.31±0.12	7.9±3.5

Abbreviations: AUC = area under the concentration-time curve; CL = clearance; C_{max} = peak concentration; n = number of subjects; SD = standard deviation; t½ = half-life; Vss = volume of distribution at steady state; y = year.

Tigecycline administered to children showed initially high concentrations, followed by rapid distribution and slower elimination. Similar to adults, CLr was relatively small compared with total CL. As has been reported for other medications, including antibiotics, in older children, CL and Vss values were lower, even when normalized for weight. The younger children also had shorter t½ values compared with older children and adults.

The clinical efficacy of tigecycline appears to be most closely related to the AUC to MIC ratio and so a reasonable dose to use in children would be one that would result in the AUC observed in adults. The MAH also presented individual listings on the PK parameters. After the recommended dose of 100 mg loading and 50 mg every 12 hours, the AUC0 24h observed in adults was approximately 5.0 mg•h/L; thus for AUC0-12H, the target would be 2.5 mg•h/L. As may be seen in Figure 1-2, children less than 12 years of age appear to need higher doses than children older than 12 years of age. For almost all children ages 12 years and older, a dose of 1 mg/kg would be expected to produce exposures of 2.5 mg•h/L or higher. Given that most children ages 12 years and older weigh at least 50 kg, the adult dose of 50 mg every 12 hours would be expected to provide appropriate exposure.

Figure 1-2: Age Versus Simulated Tigecycline Dose Needed to Cause AUC of 2.5 mg•h/L: Study 3074A1-110-US



In children less than 12 years of age, a 50-mg dose would be too much, given the smaller size of such children. Simulating exposures based upon the children studied, 1-mg/kg doses would be expected to result in a median AUC of 3.2 mg•h/L (range: 1.4-10.5 mg•h/L). In children ages 12 years and older, doses shown to be effective in adults (a 100-mg loading dose followed by 50 mg every 12 hours) would be predicted to provide a similar exposure to what was observed in adults. In children ages 8 to

11 years, doses of 1 mg/kg (maximum dose 50 mg) every 12 hours would be predicted to provide a similar exposure to what was observed in adults.

The approved dose regimen for adults with cSSTI or cIAI is an initial loading dose of 100 mg followed by 50 mg every 12 hours for 5 to 14 days. The AUC0-24h observed in adults is approximately 5.0 mg•h/L; thus, for AUC 0-12h, the target would be 2.5 mg•h/L. Dose reduction is considered necessary only for patients with severe hepatic impairment (C-P C), who receive 25 mg every 12 hours following the 100 mg loading dose.

The reasons for omitting the loading dose in children are: first, the apparently long half-life observed in adults is misleading and does not reflect the effective half-life governing the amount of accumulation observed with multiple doses. Second, the pharmacodynamic parameter predictive of clinical efficacy is AUC/MIC, which is achieved with the first dose, and does not suggest that a loading dose would provide additional effectiveness; and third, the dosing regimen in children is anticipated to be more complex than in adults and a loading dose is likely to increase the complexity further increasing dosing errors, and finally a loading dose is likely to result in tolerability issues in children. With regard to the tolerability issues, it was shown, in an integrated study of data from adult subjects, both healthy volunteers and patients with cSSSI, that higher doses and exposures were associated with decreased tolerability compared with lower doses Population pharmacokinetics/pharmacodynamic analyses of tigecycline efficacy in patients with complicated skin and ski-structure infections and safety in patients and subjects. Wyeth Research, RPT-54411, 2004; Rubino CM, Forrest A, Bhavnani S, et al. Toxicodynamic analysis in patients with hospital- or community-acquired pneumonia. 47th ICAAC 2007;Abstract A-584). The PDCO agreed that the loading dose in paediatric studies can be omitted.

The MAH initial proposal for dose recommendation based on the results of this study was to administer 50 mg every 12 hours (the same as the adult maintenance dose) to children aged 12 to 17 years old, and 1 mg/kg (up to a maximum dose of 50 mg) every 12 hours to patients 8 to 11 years old. However, CHMP could not agree on this (please refer to section "Discussions, conclusions and Benefit / Risk Assessment").

Safety

Eight subjects (32%) had treatment-emergent adverse events (TEAEs), the most frequent of which were nausea (12%), vomiting (16%), and headache (8%), with the nausea and vomiting occurring in the higher dose groups (1 mg/kg and 2 mg/kg) and considered to be possibly related to tigecycline. No deaths occurred during the study. One subject had an SAE, vomiting with associated dehydration, which resolved during a brief period of hospitalization; and 1 subject was withdrawn from the study because of a mild injection site reaction.

Study 3074K4-2207-WW

This was a phase 2, multicentre, open-label, ascending multiple-dose study to assess the pharmacokinetics, safety and tolerability of tigecycline in paediatric patients from 8 to less than 12 years of age with selected serious infections: complicated intraabdominal infections (cIAI), complicated skin and skin structure infections (cSSSI) and community acquired pneumonia (CAP). It is part of the Paediatric Investigation Plan (PIP) agreed with the PDCO and for which a positive opinion was issued by the EMA in May 2009 (date of last modification of the agreed PIP).

Eligible subjects received intravenous (IV) tigecycline at a dosage of 0.75, 1, or 1.25 mg/kg (up to a maximum dose of 50 mg) every 12 hours infused over approximately 30 minutes. Omitting the loading dose for the paediatric population was considered acceptable for the Paediatric Committee (PDCO) mainly due to tolerability issues. All subjects received IV tigecycline for a minimum of 3 days to a

maximum of 14 consecutive days. On or after day 4, it was possible to switch to oral antibiotics (IV plus oral switch). Escalation to the next dose cohort occurred only after the following: 1) safety and tolerability data at the preceding dose through the last day of therapy (tigecycline LDOT) had been reviewed by the sponsor, 2) at least 5 of the 6 properly processed PK samples were received by the central laboratory from at least 12 subjects ("PK evaluable"), and 3) all available efficacy data were reviewed.

For details on the design and results of the study please refer to the Rapporteur assessment report of procedure P46 052 from 5 July 2010 (Attachment 5).

The intent-to-treat (ITT) population consisted of 59 subjects who were screened and randomized to treatment. Of these subjects, 58 subjects received at least 1 dose of tigecycline and were included in the modified intent-to-treat (mITT) population. The disposition of subjects by treatment group and diagnosis in the mITT population is provided in the following table:

Table 1-1: Subject Disposition, mITT Population

Population, n	Tigecycline			
Diagnosis, n	0.75 mg/kg	1 mg/kg	1.25 mg/kg	Total
mITT, n	17	21	20	58
Community-acquired pneumonia, n	7	8	4	19
Complicated intra-abdominal infection, n	6	6	12	24
Complicated skin and skin structure infections, n	4	7	4	15

mITT=modified intent-to-treat.
Source: CSR-79277, Table 8-1

Overall, 53 subjects had serum tigecycline concentrations determined. Of these subjects, 47 subjects had an adequate number of PK samples to be included in the PK evaluable population: 16 subjects in the 0.75 mg/kg treatment group; 18 subjects in the 1 mg/kg treatment group; and 13 subjects were in the 1.25 mg/kg treatment group.

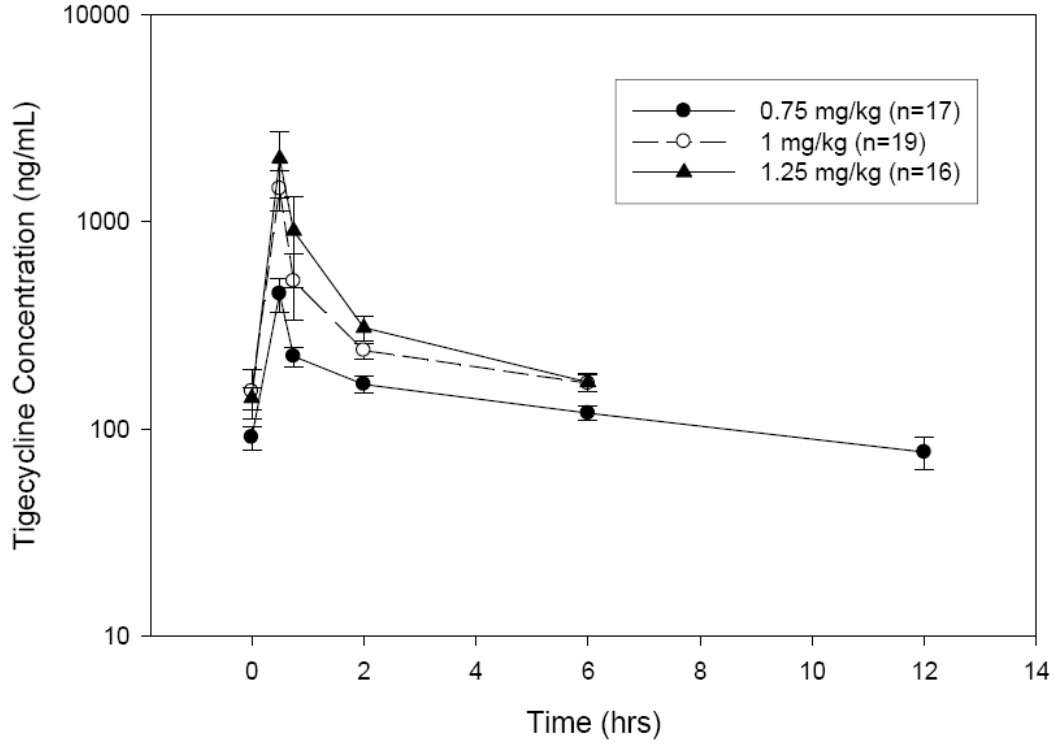
Table 4-1: Disposition of Pharmacokinetically Evaluable Subjects

Population, n	Tigecycline			
Diagnosis, n	0.75 mg/kg	1 mg/kg	1.25 mg/kg	Total
PK evaluable, n	16	18	13	47
Community-acquired pneumonia, n	7	8	3	18
Complicated intra-abdominal infection, n	6	6	7	19
Complicated skin and skin structure infections, n	3	4	3	10

PK=pharmacokinetic.
Source: Clinical Pharmacology

Tigecycline serum concentrations from a total of 53 children were collected after multiple doses of 0.75, 1 and 1.25 mg/kg. Mean ± standard error (SE) concentrations for each dosing group are shown in Figure 11-1.

Figure 11-1: Mean ± SE Steady-State Tigecycline Serum Concentrations in Children Aged 8 to 11 Years After 30-Minute Infusions Every 12 Hours



Although concentration data were available, PK parameters could not be determined for 7 children (one child in the 0.75-mg/kg group, one child in the 1-mg/kg group, and five children in the 1.25-mg/kg group). When Cmax and tmax could be reliably determined, they were. The resulting mean ± SD PK parameters determined in the 47 children who were PK evaluable are shown in Table 4-2.

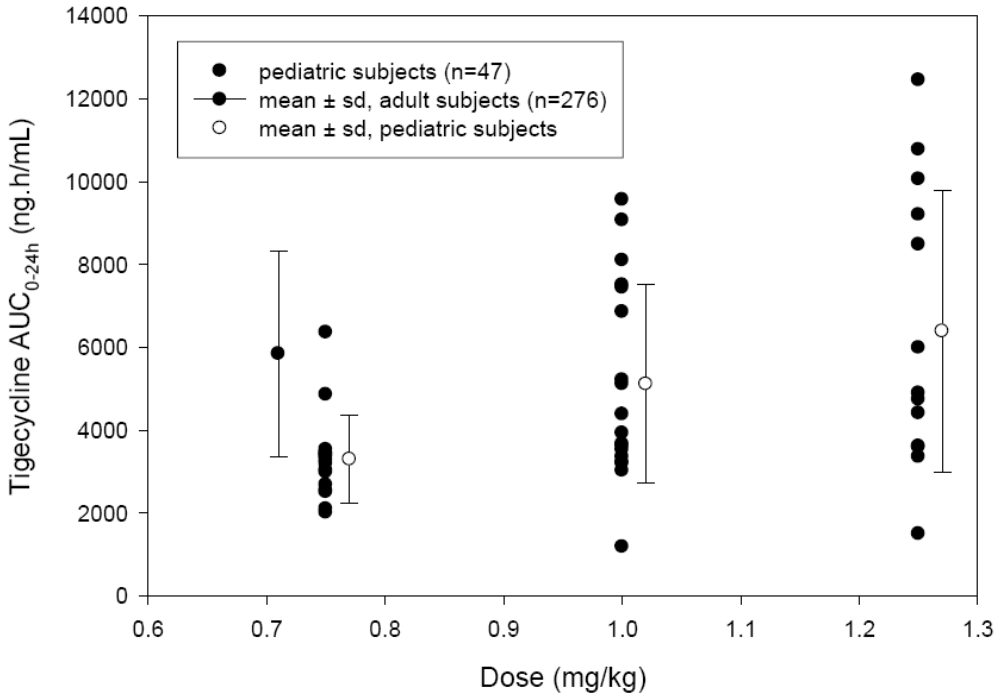
Table 4-2: Steady-state Tigecycline Pharmacokinetic Parameters in Pediatric Subjects Aged 8 to 11 Years[a]

Treatment Group Statistic	C_{max} (ng/mL)	t_{max} (hr)	AUCt (ng.h/mL)	CLW (L/hr/kg)	$V_{ss}W$ (L/kg)
0.75 mg/kg					
Mean ± SD	456 ± 347	0.6 ± 0.2	1650 ± 529	0.490 ± 0.130	7.94 ± 6.69
N	17	17	16	16	16
Min	164	0.4	1008	0.236	1.68
Median	427	0.6	1619	0.463	5.85
Max	1563	1.25	3182	0.744	26.6
1 mg/kg					
Mean ± SD	1515 ± 1457	0.5 ± 0.1	2557 ± 1196	0.498 ± 0.335	3.63 ± 2.19
N	19	19	18	18	18
Min	366	0.4	595	0.209	0.433
Median	806	0.5	2081	0.482	3.00
Max	4882	0.75	4784	1.68	7.21
1.25 mg/kg					
Mean ± SD	2599 ± 3643	0.8 ± 0.6	3196 ± 1704	0.528 ± 0.384	2.84 ± 2.78
N	16	16	13	13	13
Min	233	0	752	0.200	0.397
Median	1016	0.4	2449	0.511	2.71
Max	12900	2.27	6225	1.67	11.2
Across Treatment Groups					
Mean ± SD	1899 ±2954[a]	0.56 ± 0.18	2833 ± 1557[a]	0.503 ± 0.293	4.88 ± 4.84

a. Dose normalized to 1 mg/kg.
Source: Clinical Pharmacology

Steady-state tigecycline AUC0-24h versus dose in adults and pediatric subjects is shown in Figure 11-2. As may be seen in the figure, the AUC0-24h is slightly higher in children in the 1.25-mg/kg treatment groups, and slightly lower in children in the 1-mg/kg treatment group than the AUC0-24h observed in adult subjects with cSSSI or cIAI participating in phase 2 and 3 studies.

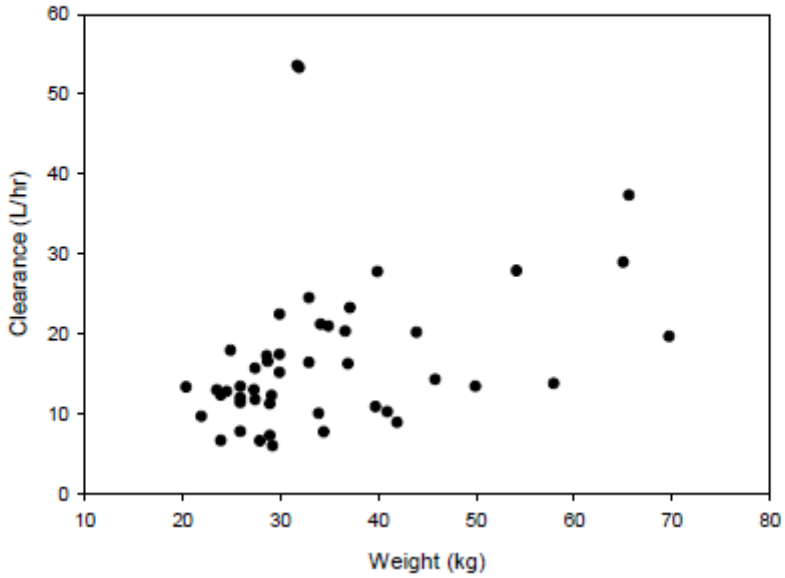
Figure 11-2: Steady-State Tigecycline $AUC_{0\text{-}24h}$ in Adult and Pediatric Subjects After IV Administration of Tigecycline Every 12 Hours



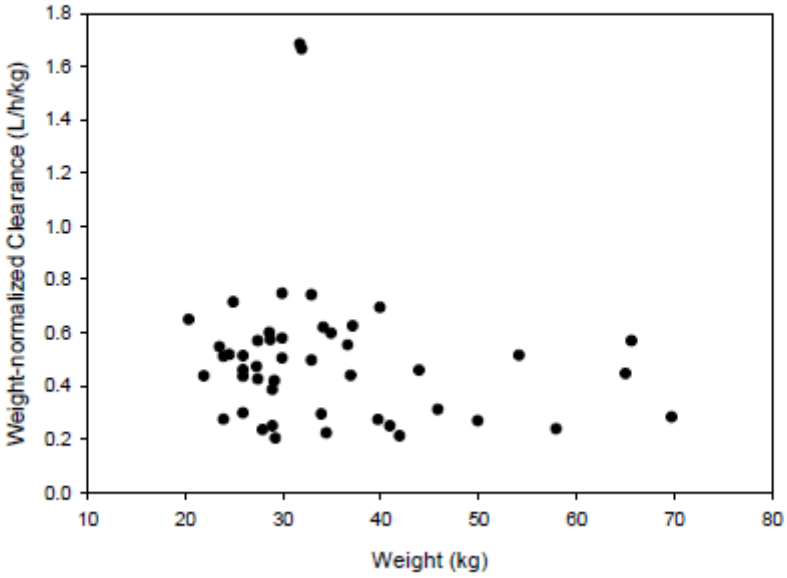
The selection of 1.2 mg/kg (maximum 50 mg per dose) BID as dosing recommendation for children 8 to 11 years old for phase 3 trials is based on the results plotted in the figure above. As AUC/MIC ratio is the PK/PD index that has been shown to correlate with efficacy, the CHMP considered that this approach was acceptable.

Plotting weight, body surface area (BSA) or body mass index (BMI) versus Clearance (CL) shows that smaller children have lower CL than larger children, but when weight, BSA, or BMI are plotted against Weight-Normalised Clearance (CLW), the apparent relationship between size and CL goes away, supporting the choice of dosing based on weight for children as may be seen in Supportive Figure 7.1 and Supportive Figure 7.2, showing weight vs CL and CLW respectively.

7.1 Weight Versus Tigecycline Clearance in Children Receiving Multiple Doses (n=47)



7.2 Weight Versus Weight-Normalized Tigecycline Clearance in Children Receiving Multiple Doses (n=47)



The percent target attainment values are shown in Table 4-3. A dose of 1.2 mg/kg, with a maximum dose of 50 mg, matches most closely the % target attainment predicted from adults participating in clinical trials.

Table 4-3: Percent Target Attainment for Various Doses in Adults and Children

Population – Dose	% Target: 6.96	% Target: 17.9
Adults – 50 mg q12h	81.6	55.5
Children – 0.75 mg/kg	70.6	38.6
Children – 1 mg/kg	77.7	49.1
Children – 1.1 mg/kg	80.0	52.2
Children – 1.2 mg/kg	81.6	54.5
Children – 1.25 mg/kg	84.9	60.2

Simulation: 10,000 replicates using data from 571 adults from Phase 2 and 3 studies in cIAI, cSSSI, CAP and 47 children from P2207.
Source: Clinical Pharmacology

Although the MAH conclusion was that 1.2 mg/kg twice daily would be an appropriate dose to be tested in further clinical studies in children the CHMP was not convinced and the MAH was requested to address several other issues (please refer to section "Discussions, conclusions and Benefit / Risk Assessment").

Safety

Treatment-Emergent Adverse Event Data (TEAEs)

An AE was considered treatment emergent if it emerged during the on-therapy period but was absent before treatment, or worsened during the treatment period relative to the pretreatment state. AEs that occurred within 5 days after the last test article administration were attributed to the on-therapy period.

Overall, 44 (75.9%) subjects were reported with 1 or more TEAEs. TEAEs were most commonly associated with the digestive system. The most frequently occurring TEAE was nausea, reported in 28 (48.3%) subjects overall, and in a significantly higher percentage of subjects in the 1.25-mg/kg group (60.0%) compared with the 0.75-mg/kg group (17.6%; p=0.018), and in the 1 mg/kg group (61.9%) compared with the 0.75-mg/kg group (17.6%; p=0.009). Vomiting was the second mostly frequently reported TEAE, reported in 27 (46.6%) subjects overall. Vomiting was reported in the 0.75-mg/kg group in 5 children (29%) while in the 1-mg/kg and 1.25-mg/kg groups these figures were 11 (52.4%) and 11 (50%), respectively.

Nine subjects with CAP (47.4%) were reported with 1 or more TEAEs. The most frequently occurring TEAE was nausea, reported in 8 (42.1%) subjects overall, and in a significantly higher percentage of subjects in the 1.25-mg/kg group (100.0%) compared with the 0.75-mg/kg group (14.3%; p=0.015). Vomiting, reported in 5 (26.3%) subjects overall, was reported significantly more frequently in the 1.25-mg/kg group (75.0%) compared with the 0.75-mg/kg group (0%; p=0.024).

Twenty (20, 83.3%) subjects with cIAI were reported with 1 or more TEAEs. The most frequently occurring AEs were vomiting, reported in 15 (62.5%) subjects overall, and nausea, reported in 9 (37.5%) subjects overall.

One (1) or more TEAEs were reported in all 15 subjects with cSSSI (100%). TEAEs were most commonly associated with the digestive system. The most frequently occurring TEAEs were nausea, reported in 11 (73.3%) subjects overall, and vomiting, reported in 7 (46.7%) subjects overall. Nausea was reported significantly more frequently in the 1-mg/kg group (100%) compared with the 0.75-mg/kg group (25.0%; p=0.024).

Overall, significantly more subjects in the 1.25-mg/kg (60.0%) and 1-mg/kg (61.9%) groups reported TEAEs of nausea compared with subjects in the 0.75-mg/kg group (17.6%; p=0.018 and p=0.009, respectively). Among subjects with CAP, significantly more subjects in the 1.25-mg/kg group compared with subjects in the 0.75-mg/kg group reported TEAEs of nausea (100% versus 14.3%,

p=0.015) and vomiting (75.0% versus 0%, p=0.024). Among subjects with cSSSI, significantly more subjects in the 1-mg/kg group reported TEAEs of nausea (100%) compared with subjects in the 0.75-mg/kg group (25.0%, p=0.024). Among subjects with cIAI, there were no significant differences between treatment groups in the incidences of nausea or vomiting.

The incidences of nausea and vomiting across treatment groups is summarized overall and by diagnosis in Table 10-2 below.

Table 10-2: Number (%) of Subjects Reporting Treatment-Emergent Adverse Events of Nausea or Vomiting by Diagnosis, mITT Population

Population System Organ Class[a] Preferred Term	Overall p-Value[b]	Tigecycline 0.75mg/kg	Tigecycline 1 mg/kg	Tigecycline 1.25 mg/kg	Tigecycline Total
mITT, n		n=17	n=21	n=20	n=58
Any adverse event	0.153	7 (41.2)	15 (71.4)	13 (65.0)	35 (60.3)
Gastrointestinal disorders	0.153	7 (41.2)	15 (71.4)	13 (65.0)	35 (60.3)
Nausea	0.010**	3 (17.6)	13 (61.9)	12 (60.0)	28 (48.3)
Vomiting	0.272	5 (29.4)	11 (52.4)	11 (55.0)	27 (46.6)
Community-acquired pneumonia, n		n=7	n=8	n=4	n=19
Any adverse event	0.024*	1 (14.3)	3 (37.5)	4 (100)	8 (42.1)
Gastrointestinal disorders	0.024*	1 (14.3)	3 (37.5)	4 (100)	8 (42.1)
Nausea	0.024*	1 (14.3)	3 (37.5)	4 (100)	8 (42.1)
Vomiting	0.025*	0	2 (25.0)	3 (75.0)	5 (26.3)
Complicated intra-abdominal infections, n		n=6	n=6	n=12	n=24
Any adverse event	0.314	5 (83.3)	5 (83.3)	6 (50.0)	16 (66.7)
Gastrointestinal disorders	0.314	5 (83.3)	5 (83.3)	6 (50.0)	16 (66.7)
Nausea	0.637	1 (16.7)	3 (50.0)	5 (41.7)	9 (37.5)
Vomiting	0.424	4 (66.7)	5 (83.3)	6 (50.0)	15 (62.5)
Complicated skin and skin structure infections, n		n=4	n=7	n=4	n=15
Any adverse event	0.025*	1 (25.0)	7 (100)	3 (75.0)	11 (73.3)
Gastrointestinal disorders	0.025*	1 (25.0)	7 (100)	3 (75.0)	11 (73.3)

Table 10-2: Number (%) of Subjects Reporting Treatment-Emergent Adverse Events of Nausea or Vomiting by Diagnosis, mITT Population (Cont'd)

Population System Organ Class[a] Preferred Term	Overall p-Value[b]	Tigecycline 0.75mg/kg	Tigecycline 1 mg/kg	Tigecycline 1.25 mg/kg	Tigecycline Total
Nausea	0.025*	1 (25.0)	7 (100)	3 (75.0)	11 (73.3)
Vomiting	0.804	1 (25.0)	4 (57.1)	2 (50.0)	7 (46.7)

mITT=modified intent-to-treat.

a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report 2 or more different adverse events within the higher level category.

b. Overall p-value refers to the number of subjects with data. Fisher exact test p-value (2-tail). Statistical significance at the .05, .01, .001 levels is denoted by *, **, ***, respectively.

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).

Source: Supportive Table 15.26 and Supportive Table 15.27.

Deaths

No subjects died during the study.

Serious Adverse Events

A summary of SAEs by body system and diagnosis is provided in Table 10-3 below. A total of 3 (5.2%) subjects were reported with SAEs during the study. No SAEs were reported in subjects with CAP. One (1; 4.2%) subject with cIAI receiving 0.75 mg/kg of tigecycline had an SAE of postoperative wound infection. Two (2; 13.3%) subjects with cSSSI had SAEs: 1 subject in the 1-mg/kg group had an SAE of anal fistula and 1 subject in the 1.25-mg/kg group had an SAE of abdominal pain. All SAEs were resolved.

Table 10-3: Number (%) of Subjects Reporting Serious Adverse Events by Diagnosis, mITT Population

Population System Organ Class[a] Preferred Term	Overall p-Value[b]	Tigecycline 0.75mg/kg	 1 mg/kg	 1.25 mg/kg	 Total
mITT, n		n=17	n=21	n=20	n=58
Any adverse event	1.000	1 (5.9)	1 (4.8)	1 (5.0)	3 (5.2)
Gastrointestinal disorders	1.000	0	1 (4.8)	1 (5.0)	2 (3.4)
Abdominal pain	0.638	0	0	1 (5.0)	1 (1.7)
Anal fistula	1.000	0	1 (4.8)	0	1 (1.7)
Infections and infestations	0.293	1 (5.9)	0	0	1 (1.7)
Postoperative wound infection	0.293	1 (5.9)	0	0	1 (1.7)
Community-acquired pneumonia, n		n=7	n=8	n=4	n=19
Any adverse event		0	0	0	0
Complicated intra-abdominal infections, n		n=6	n=6	n=12	n=24
Any adverse event	0.500	1 (16.7)	0	0	1 (4.2)
Infections and infestations	0.500	1 (16.7)	0	0	1 (4.2)
Postoperative wound infection	0.500	1 (16.7)	0	0	1 (4.2)
Complicated skin and skin structure infections, n		n=4	n=7	n=4	n=15
Any adverse event	1.000	0	1 (14.3)	1 (25.0)	2 (13.3)
Gastrointestinal disorders	1.000	0	1 (14.3)	1 (25.0)	2 (13.3)
Abdominal pain	0.533	0	0	1 (25.0)	1 (6.7)
Anal fistula	1.000	0	1 (14.3)	0	1 (6.7)

mITT=modified intent-to-treat.

a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report 2 or more different adverse events within the higher level category.

b. Overall p-value refers to the number of subjects with data. Fisher exact test p-value (2-tail). Statistical significance at the .05, .01, .001 levels is denoted by *, **, ***, respectively.

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).

Source: /CLINICAL R&D/CLINICAL PROGRAMMING SAS REPORTS/3074K4 /2207/FINAL CDRs/ ae5_s.html 15OCT09 11:38 and ae5_s_diag.html 15OCT09 11:38

Safety-Related Discontinuations

A summary of AEs resulting in withdrawal from the study is provided in Table 10-4 overall and by diagnosis. Overall, 2 (3.4%) subjects were withdrawn from the study because of AEs. Among subjects with cIAI, 1 subject in the 1-mg/kg group was withdrawn from the study because of AEs of pancreatitis, blood amylase increased, and lipase increased, and 1 subject in the 1.25-mg/kg group was withdrawn from the study because of an AE of lipase increased.

Table 10-4: Number (%) of Subjects Reporting Adverse Events Resulting in Withdrawal From the Study by Diagnosis, mITT Population

Population System Organ Class[a] Preferred Term	Overall p-Value[b]	Tigecycline 0.75mg/kg	 1 mg/kg	 1.25 mg/kg	 Total
mITT, n		n=17	n=21	n=20	n=58
Any adverse event	1.000	0	1 (4.8)	1 (5.0)	2 (3.4)
Gastrointestinal disorders	1.000	0	1 (4.8)	0	1 (1.7)
Pancreatitis	1.000	0	1 (4.8)	0	1 (1.7)
Investigations	1.000	0	1 (4.8)	1 (5.0)	2 (3.4)
Blood amylase increased	1.000	0	1 (4.8)	0	1 (1.7)
Lipase increased	1.000	0	1 (4.8)	1 (5.0)	2 (3.4)
Community-acquired pneumonia, n		n=7	n=8	n=4	n=19
Any adverse event		0	0	0	0
Complicated intra-abdominal infections, n		n=6	n=6	n=12	n=24
Any adverse event	1.000	0	1 (16.7)	1 (8.3)	2 (8.3)
Gastrointestinal disorders	0.500	0	1 (16.7)	0	1 (4.2)
Pancreatitis	0.500	0	1 (16.7)	0	1 (4.2)
Investigations	1.000	0	1 (16.7)	1 (8.3)	2 (8.3)
Blood amylase increased	0.500	0	1 (16.7)	0	1 (4.2)
Lipase increased	1.000	0	1 (16.7)	1 (8.3)	2 (8.3)
Complicated skin and skin structure infections, n		n=4	n=7	n=4	n=15
Any adverse event		0	0	0	0

mITT=modified intent-to-treat.

a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report 2 or more different adverse events within the higher level category.

b. Overall p-value refers to the number of subjects with data. Fisher exact test p-value (2-tail). Statistical significance at the .05, .01, .001 levels is denoted by *, **, ***, respectively.

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).

Source: /CLINICAL R&D/CLINICAL PROGRAMMING SAS REPORTS/3074K4 /2207/FINAL CDRs/ ae5_w.html 15OCT09 11:38 and ae5_w_diag.html 15OCT09 11:38

Additionally, three subjects were withdrawn from the study due to post-operative wound infection (cIAI, 0.75 mg/kg group), anal fistula (cSSTI, 1 mg/kg group) and severe abdominal pain (cSSTI, 1.25 mg/kg group.

Comparison between the two PK studies

A comparison of the study designs and observed pharmacokinetic parameters was requested by the CHMP and is shown in Table 8-1.

Table 8-1: Comparison of Tigecycline Pharmacokinetic Studies in Children

Design or Parameter	Study 110-US		Study 2207-WW
Study Design			
Subject condition	Recovering from infections		Newly diagnosed infection
Age (number with PK)	8 – 11 yr (n=7) 12 – 16 yr (n=16)		8 – 11 yr (n=47)
Tigecycline dose	0.5, 1, 2 mg/kg single dose (no dose limit) administered IV over 30 minutes		0.75, 1, 1.25 mg/kg, (maximum 50 mg) every 12 h administered IV over 30 minutes
Drug concentration measurement	0, 0.5, 0.75, 1, 2, 4, 8, 12, 24, 36, 48 h after start of infusion		0 – before drug given; then on day 3: 0, 0.5, 2, 6, 12 h after the start of the infusion initially, then with protocol amendment 0, 0.5, 0.75, 2, 6 h after the start of the infusion.
PK Parameter (mean ± sd)	***12 – 16 years***	***8 – 11 years***	***8 – 11 years***
C_{max}[a] (ng/mL)	8508 ± 11433	3881 ± 6637 1581 ± 1422[c]	1899 ± 2954
T_{max} (h)	0.52 ± 0.06	0.5 ± 0	0.56 ± 0.18
$T_{½}$ (h)	21.7 ± 6.2	16.6 ± 5.4	--
AUC[a,b](ng h/mL)	7026 ± 4088	4034 ± 2874 3116 ± 1331[c]	2833 ± 1557
CLW (L/h/kg)	0.194 ± 0.150	0.349 ± 0.201	0.503 ± 0.293
VssW (L/kg)	3.93 ± 3.39	5.66 ± 2.66	4.88 ± 4.84

Abbreviations: AUC=area under the concentration curve, CLW=weight-normalized clearance, C_{max}=maximum concentration, PK=pharmacokinetic, $T_{½}$ = half life, T_{max}=time to maximum concentration, VssW= weight-normalized volume of distribution.

a. Normalized to 1 mg/kg
b. $AUC_{0\text{-infinity}}$ for single dose, $AUC_{0\text{-tau}}$ for multiple dose
c. Omitting subject 11

The pharmacokinetic parameters observed in the children age 8 to 11 years were comparable between the 2 studies. Study 110-US was a small study and enrolled only 7 children aged 8 to 11, one of whom had a very high Cmax (19980 ng/mL) that may have been due to a contaminated sample. Three (3) of the 16 children aged 12 to 16 years had very high Cmax values as well, leading to the highly variable estimates of Cmax. The AUC values observed in the 8 to 11 year olds were comparable when the high values were excluded.

The CHMP also requested the MAH to provide a population pharmacokinetic analysis with the two PK studies conducted in the paediatric population. A model of tigecycline pharmacokinetics was derived from the pooled data. The pharmacokinetic data were best described using a linear two compartment model with an effect of weight on clearance. No other covariates were identified as being predictive of tigecycline pharmacokinetics. The data were variable, particularly peak concentrations which gave rise to high residual variability in the final model. The model under-predicts Cmax, i.e. the experimental Cmax concentrations are higher than those predicted by the model. The evaluation of the final model showed no overall bias or substantial model misspecification.

The identification of weight on clearance is supportive of a weight based dose regimen for the paediatric population although the relationship between weight and clearance (and hence AUC) is not linear. According to the MAH, paediatric subjects receiving 1 mg/kg doses would be predicted to show increasing exposure of approximately 40%, over the range of body weights of 20 to 50 kg, followed by gradually decreasing exposure due to the dose capping at 50 mg.

In the answers to CHMP's second RSI, the MAH has clarified clarified that the simulated mean AUC0-24h following a dose of 0.75 mg/kg is below the adult AUC0-24h target of 5 mg•h/L while for the dose of 1.2 mg/kg the mean values are usually above this target and has confirmed that 1.2 mg/kg (up to a maximum of 50 mg twice daily) administered every 12 hours infused over 30 to 60 minutes is the dose to be further tested in children and adolescents 8 to less than 18 years old. The CHMP considered this to be acceptable, although modelling and simulation along with the safety data may have supported

the 1 mg/kg dose, but agreed that appropriate measures were already agreed with the PDCO to be put in place in the planned phase 3 studies in children (DSMB, stopping rules) to limit the exposure of children to inappropriate doses.

Changes to the Product Information

Following the assessment of CHMP the MAH agreed to update the Tygacil SmPC as follows:

Section 4.2

[…]

Paediatric population

The safety 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).~~ (see section 4.4). Only pharmacokinetic data are available (see section 5.2).

Section 4.8

[…]

Paediatric population

Very limited safety data were available from a multiple dose PK study (see section 5.2). No new or unexpected safety concerns were observed with tigecycline in this study.

Section 5.2.

Paediatric Population

~~The pharmacokinetics of tigecycline in patients less than 18 years of age has not been established (see section 4.2).~~ The safety and efficacy of tigecycline in the paediatric population 8 to <18 years of age have not been established.

Tigecycline pharmacokinetics was investigated in two studies. The first study enrolled children aged 8-16 years (n=24) who received single doses of tigecycline (0.5, 1, or 2 mg/kg, with no dose limitation) administered intravenously over 30 minutes. The second study was performed in children aged 8 to 11 years (n=47) who received multiple doses of tigecycline (0.75, 1, or 1.25 mg/kg up to a maximum dose of 50 mg) every 12 hours administered intravenously over 30 minutes. No loading dose was administered in these studies. The pharmacokinetic parameters may be observed in the table below.

Dose Normalized to 1 mg/kg Mean ± SD Tigecycline Cmax and AUC in Children			
Age (yr)	*N*	*Cmax (ng/mL)*	*AUC (ng.h/mL)**
Single dose			
8 – 11	*8*	*3881 ± 6637*	*4034 ± 2874*
12 - 16	*16*	*8508 ± 11433*	*7026 ± 4088*
Multiple dose			
8 - 11	*47*	*1899 ± 2954*	*2833 ± 1557*
** single dose $AUC_{0-\infty}$, multiple dose AUC_{0-12h}*			

The target AUC0-12h in adults after the recommended dose of 100 mg loading and 50 mg every 12 hours, was approximately 2500 ng•h/mL.

Discussions, conclusions and Benefit / Risk Assessment

This type II variation initially aimed at amending section 5.2 of the approved SmPC for Tygacil by providing PK data on tigecycline in the paediatric population and was requested by the CHMP in January 2011, during the assessment of study 3074K4-2207-WW. The initial proposal made by the MAH to update section 5.2 of the Tygacil SmPC was not considered acceptable by the CHMP. CHMP adopted on 23 June 2011 a RSI requesting the MAH to also update sections 4.2 and 4.8 of the SmPC with a summary of the safety data of the paediatric PK studies.

The MAH initial proposal for dose recommendation based on the results of 3074A1-110-US study for the planned phase 3 trials in children was to administer 50 mg every 12 hours (the same as the adult maintenance dose) to children aged 12 to 17 years old, and 1 mg/kg (up to a maximum dose of 50 mg) every 12 hours to patients 8 to 11 years old. However, the CHMP could not agree on this due to the following issues:

- there were only 8 subjects aged 8-11 years enrolled of which two received the 1 mg/kg dose and the other six received 0.5 mg/kg. The observed Cmax and AUCs were lower with 1 mg/kg than with 0.5 mg/kg in this age group (see table above), but this observation is not explored (e.g. in terms of subject demographics) in the study report. Because the differences in CL and weight-normalized CL values were greater than the change in weight-normalized Vss values, the λz was also higher in younger children and so t½ was longer. Age, weight and BMI were significant factors for weight-normalised clearance, but not for weight-normalised Vss, in the univariate regression model analyses.

- for the US children enrolled in this study the mean weight in the 8-11 years group was around 50 kg (max 64 kg) and the mean weight in the older subjects was 60-70 kg. Also, the modelling suggested that in those aged 8-11 years 1 mg/kg every 12 hours would give a median AUC of 3.2 mg•h/L but with a range from 1.4-10.5 mg•h/L.

Therefore, the CHMP concluded that the evidence to support the dose regimen proposed for future trials enrolling children aged < 12 years and/or < 50 kg was weak and needed much more investigation. As a consequence, the MAH performed study 3074K4-2207-WW (study 2207) in children from 8 to less than 12 years old. The CHMP agreed with the MAH's proposal not to develop a specific formulation for the paediatric population, but to use the one currently marketed for adults in study 2207.

Regarding study 2207, although the MAH conclusion was that 1.2 mg/kg twice daily would be an appropriate dose to be tested in further clinical studies in children the CHMP was not convinced and the MAH was requested to address several issues. First, the issue of the linearity of Cmax, as this PK parameter increases more than proportionally with higher doses (e.g. from a mean of 456 ng/ml in the 0.75 mg/kg group to 2599 ng/ml in the 1.25 mg/kg group). The appropriateness of normalising clearance by body weight, i.e. weight-normalized clearance (CLW) was consequently raised by CHMP, taking into account the lack of proportionality in Cmax and other issues related to the calculation of $AUC_{0\text{-}24h}$ such as the lack of sampling times at 12 hours (as $AUC_{0\text{-}24h}$ was calculated by doubling the AUCτ). Similarly, the MAH was requested to provide the individual clearance values (CL) by dosing group and overall, and plots of weight, BMI and age vs. CL and CLW by dosing group. Furthermore, a population pharmacokinetic analysis of both paediatric trials was requested by CHMP.

According to the information provided by the MAH in its responses to the first CHMP RSI, no firm conclusion on linearity could be drawn based on the Cmax values reported from study 2207, due to sample timing issues. As Cmax values higher than expected have been observed in both paediatric PK

trials, incomplete distribution as a consequence of the short time of infusion could also be an alternative explanation. The CHMP considered that it was advisable to prolong the time of infusion to 60 minutes in further paediatric trials. Additional data provided in response to the CHMP questions suggested that clearance is not dependent on the dose administered, but is mainly related to body weight (i.e. in smaller children clearance is lower), although the variability in clearance explained by body weight seems limited, while no influence of age or dose is observed (within the narrow age range and dosing regimens studied in study 2207).

From a safety perspective CHMP agreed that no new safety signals have arisen with regards to what had been observed in adults with the exception of QTc prolongation in a child in the 1-mg/kg group that has been reported as probably related to tigecycline. At CHMP request, the MAH provided the case narrative. As QTc prolongation is considered as a potential risk in the safety specifications of the Risk Management Plan of Tygacil, the CHMP agreed that no further actions were necessary as this adverse event is reviewed in the PSURs.

The MAH performed an exposure-safety relationship analysis and concluded that there is no contribution of tigecycline Cmax or AUC0-24h to the occurrence of nausea or vomiting. However, CHMP considers that what the raw data show is that nausea and vomiting are dose-dependent.

Based on the data presented by the MAH the CHMP agreed to the inclusion of the above pharmacokinetic and safety data from the PK paediatric trials in sections 4.2, 4.8 and 5.2 of the Tygacil SmPC.

Considering the newly available data on the adverse events from the above paediatric studies in connection with an appropriate update of the Product information to reflect them, the CHMP considered that the benefit–risk remains positive.

4. Conclusion

On 21 July 2011 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics

- To update sections 4.2, 4.8 and 5.2 of the Tygacil SmPC with paediatric PK and safety information based on the assessment of paediatric studies 3074K4-2207-WW and 3074A1-110-US, both previously submitted and assessed. This variation was requested by the CHMP on 20 January 2011.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

EPAR scope:

To update sections 4.2, 4.8 and 5.2 of the Tygacil SmPC with paediatric PK and safety information based on the results of paediatric studies 3074K4-2207-WW and 3074A1-110-US, both submitted and assessed in previous procedures. This variation was requested by the CHMP on 20 January 2011.

Summary / scientific discussion:

Additional data from an open label, single, ascending dose study conducted in children aged 8-16 years and aiming to characterize the pharmacokinetics and safety/tolerability of single intravenous doses

(0.5 mg/kg, 1 mg/kg and 2 mg/kg) of tigecycline and a phase 2, multicentre, open-label, ascending multiple-dose study to assess the pharmacokinetics, safety and tolerability of tigecycline in paediatric patients from 8 to less than 12 years of age with selected serious infections: complicated intraabdominal infections (cIAI), complicated skin and skin structure infections (cSSSI) and community acquired pneumonia(CAP) lead to an update of the Tygacil SmpC with a synopsis of the PK parameters from the two studies and with the information that the safety data observed in the multiple-dose PK study, (although limited due to the small number of children enrolled and to the fact that 3 doses were tested) was consistent with the type of adverse events already reported by adult patients such as nausea, vomiting, pancreatitis etc. Overall, the CHMP agreed that safety and efficacy of tigecycline in children needs to be demonstrated and agreed to include the new paediatric data in the Tygacil SmPC.

6. Attachments

1. SmPC (changes highlighted) as adopted by the CHMP on 21 July 2011.
2. Rapporteur's variation assessment report circulated on 6 June 2011.
3. Rapporteur's final assessment report circulated on 20 June 2011.
4. Request for supplementary information and extension of timetable adopted by the CHMP on 23 June 2011.
5. Rapporteur's assessment report on procedure P46 052 from 5 July 2010
6. Rapporteur's preliminary assessment report on the MAH's responses circulated on 11 July 2011.
7. Rapporteur's updated assessment report on the MAH's responses circulated on 18 July 2011.

Attachment 1

SmPC (changes highlighted) as adopted by the CHMP on 21 July 2011.

Attachment 2

Rapporteur's variation assessment report circulated on 6 June 2011.

Attachment 3

Rapporteur's final assessment report circulated on 20 June 2011.

Attachment 4

Request for supplementary information and extension of timetable adopted by the CHMP on 23 June 2011.

Attachment 5

Rapporteur's assessment report on procedure P46 052 from 5 July 2010

Attachment 6

Rapporteur's preliminary assessment report on the MAH's responses circulated on 11 July 2011.

Attachment 7

Rapporteur's updated assessment report on the MAH's responses circulated on 18 July 2011.