ABSTRACT

Title

Prospective, observational cohort, evaluating the incidence of nephrotoxicity and other adverse events of interest in patients treated with the higher recommended teicoplanin loading dose (12 mg/kg twice a day [BID]), and comparison with external historical comparator data.

Keywords

Teicoplanin, loading dose, nephrotoxicity

Rationale and background

Teicoplanin is a glycopeptide antibiotic, marketed in Europe since 1988 (first approved for marketing in Italy as Targosid® on 30 July 1987, and as Targocid® in other countries), commonly used for the parenteral treatment of the following infections: complicated skin and soft tissue infections, bone and joint infections, hospital acquired pneumonia, community acquired pneumonia, complicated urinary tract infections, infective endocarditis, peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD), bacteremia that occurs in association with any of the above indications. Teicoplanin is also indicated as an alternative oral treatment for *Clostridium difficile* infection-associated diarrhea and colitis (1).

An Article 30 referral procedure EMEA/H/A-30/1301 was initiated in November 2011 (2) in order to resolve divergences amongst the nationally authorized Summary of Product Characteristics (SmPC) for Targocid and associated names and thus to harmonize its divergent SmPCs across Europe (EU). During the referral Article 30 procedure, the MAH proposed the loading dose of 12 mg/kg twice a day (BID) for severe infections based on Monte-Carlo simulations conducted by Yamada et al (3) suggesting that loading doses of 6 mg/kg BID for 3 administrations for most infections, and 12 mg/kg BID for 3 to 5 administrations should be considered for severe infections such as endocarditis, bone and joint infections. This loading dose of 12 mg/kg BID is currently recommended in the European harmonized SmPC adopted by the Committee for Medicinal Products for Human Use (CHMP) within the Article 30 referral. A warning was included in sections 4.4 and 4.8 of the SmPC that patients should be especially monitored for adverse reactions when the higher dosage of 12 mg/kg BID is administered.

During this referral Article 30 procedure, a Post Authorization Safety Study (PASS) was requested by the CHMP, endorsed by the European Commission (EC) on 12 September 2013, in order to evaluate the safety of the higher loading dose (HLD) of teicoplanin 12 mg/kg BID (24 mg/kg/day), considering that the safety data available for this loading dose was limited. As a consequence of the referral evaluation, the agreed PASS was mentioned in the Annex IV of the European Commission decision (dated 12 September 2013) as a condition to the Marketing Authorization.

Subsequent to the EC Decision and according to the European regulatory procedure, in line with the conclusion of this referral procedure, the PASS protocol “Prospective, observational cohort, non-comparative study describing the safety profile of the higher recommended

teicoplanin loading dose of 12 mg/kg twice a day" was submitted to the Pharmacovigilance Risk Assessment Committee (PRAC) on 21 October 2013.
The initial version of the protocol was endorsed by the PRAC on 11 June 2015.
The amended protocol (amendment 1) included changes to comply with the request of the Central Italian Ethics Committee (dated November 2015 and confirmed in March 2016).

The amendment 1 was endorsed by the PRAC on 5 May 2017.

The amended protocol (amendment 2) lengthened the inclusion period of 6 additional months. The amendment 2 was endorsed by the PRAC on 17 May 2018.

Research question and objectives Study

The main objective of this study was to estimate the nephrotoxicity potential of the higher loading dose of teicoplanin, utilizing real world clinical practice data. The estimated incidence rates from this study were to be compared to external historical incidence rates for nephrotoxicity associated with vancomycin high dose and with teicoplanin lower loading doses from literature data, as requested by the PRAC.

Teicoplanin is characterized by a long elimination half-life (100 to 170 hours [about 4 to 8 days]), therefore, it takes a long time to reach a steady-state concentration. As a consequence, initial loading dose regimen was recommended by the MAH for teicoplanin to promptly reach the target trough plasmatic concentration (2). Different doses and intervals of administrations were proposed to reach predefined targeted trough levels depending on the type of infection, the nature and the susceptibility of the pathogen and on the patient status. The higher loading dose of 12mg/kg BID for 3 to 5 administrations is recommended for bone and joint infections and for infective endocarditis. Trough concentrations >20mg/L (fluorescence polarization immunoassay [FPIA]) should be targeted for bone and joint infections, and trough concentrations of 30-40mg/L [FPIA] should be targeted for infective endocarditis and other severe infections (2, 3).

Teicoplanin exhibits tri-phasic plasma disposition profile (4, 5), with the first distribution phase, with $t_{1/2}$ of around 0.4 to 1 hours, occurring immediately after C_{max} and of short duration, the second distribution/elimination phase with $t_{1/2}$ of 5 to 15 hours occurring roughly up around 24 hours after dosing and the terminal elimination phase ($t_{1/2}$ of 80 to 170 hours) occurring roughly from 24 hours post-dose. Accordingly, for the BID or once a day (OD) regimen, for the trough samples taken within a few hours before the next dose, limited variations in teicoplanin concentrations are expected given the predominant 2nd disposition phase, with $t_{1/2}$ of 5 to15 hours, occurring over this period of time. Considerable variation in teicoplanin pharmacokinetic parameters was reported, hence the lack of correlation between doses administered and the corresponding plasma concentrations (6, 7).

The overall duration of treatment with teicoplanin was not given precisely since it should be adjusted individually, according to the underlying type and severity of infection and the clinical response of the patient (8, 9). Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Since the safety data for the loading dose of 12 mg/kg BID (24 mg/kg/day) was limited, the MAH agreed to the request made by the CHMP, and endorsed by the European Commission on 12 September 2013, to perform a non-interventional post authorization safety study

(PASS) to evaluate the safety of teicoplanin in adults with Gram-positive infections who are exposed to the higher loading dose of 12 mg/kg BID (24 mg/kg/day). Prospective collection of adverse events was planned to allow a thorough evaluation of the safety profile of teicoplanin regimens. The data were to be prospectively collected until teicoplanin treatment discontinuation and for 60 days after teicoplanin discontinuation.

Targocid and associated names are referred to as “teicoplanin” across this document.

Study Design

This study was a non-interventional prospective study, involving primary data collection, in which the data collected originate from routine clinical care.

This non-interventional study protocol fulfilled the following requirements (10):

- The medicinal product was to be prescribed in the usual manner in accordance with the terms of the marketing authorization,
- The assignment of the patient to a particular therapeutic strategy was not decided in advance by the trial protocol, but felt within current practice and the prescription of the medicine was clearly separated from the decision to include the patient in the study; and,
- No additional diagnostic or monitoring procedures were to be applied to the patients and epidemiological methods were used for the analysis of collected data.

The study was to be conducted in several European countries using teicoplanin high loading dose, as described in the approved SmPC. The estimated enrollment period was 2 years and 6 months, to allow for recruitment of 300 patients. The enrollment period could vary in different countries depending on the Independent Ethics Committee (IEC) process in each country.

The study included:
- a loading dose period (up to 3 days). The duration of the loading dose period was defined based on teicoplanin' SmPC recommendation for the 12 mg/kg BID dose, ie, 3 to 5 administrations for severe infections such as endocarditis or bone and joint infections;
- a maintenance dose period, depending upon completion of the planned teicoplanin regimen duration for each individual patient;
- and a follow-up (FU) period of 60 days after the last administration of teicoplanin.

The following periods were defined for the statistical analysis:
- a loading dose analysis period, up to day 10
- a maintenance dose analysis period, from the end of the loading dose analysis period up to the last administration of teicoplanin
- a FU analysis period of 60 days after the last administration of teicoplanin.

The investigators were asked to enter patient’s data into the eCRF: at Inclusion Visit 1 (Day 1), Visit 2 (End of Loading Dose period), Visit 3 (Day 10-end of the loading dose analysis period), Visit 4 (end of treatment (EOT)) and Visit 5 (end of study visit (EOS)). In case of early discontinuation and/or at the end of teicoplanin treatment, the end of treatment page was to be completed.

Setting

- Site and patient selection:
  - The Investigators were identified by country based on data issued from prescription records: centers with high usage of the higher loading dose of teicoplanin were contacted for selection. Only countries prescribing the higher dose of teicoplanin were selected for participation in this study: Germany, Italy, France, Poland, Romania, and the UK. The following wards were identified as participating sites: Intensive care units, Infectious disease units and Septic surgery units.
  - The study population was to consist of adult patients (≥18 years old) with infection types for which the higher loading dose of teicoplanin was approved, who were receiving a teicoplanin high loading dose of 12 mg/kg twice a day (24 mg/kg/day), as prescribed by the treating physician. All patients fulfilling the "inclusion / exclusion" criteria and willing to participate were eligible for the study (informed consent form signed by the patient or by the patient's representative). The enrollment was done consecutively without any potential for selection bias. No additional selection criteria were applied.
- Overall participation status: The number of participating centers; of active centers and of patients included was described globally and by country.
- Data collection: The patient data were collected primarily from patient's hospital source dossiers by the Investigators or site personnel via electronic Case Report Form (eCRF). Information reported in the eCRF was compared with the original data from source documents in accordance with the study manual to ensure that the information collected was complete, accurate and valid. If the investigators delegated their responsibility for the eCRF completion to another person, the name, position of this person should be supplied to the sponsor to request a specific access with code for this person. A log-in and a password were provided to all authorized eCRF users.
- Safety data collection: The eCRF allowed for targeted data collection on the chosen endpoints, eg, the eCRF asked for occurrence of hearing and balance/vestibular disorders at each visit, in addition to the other adverse events of interest. Information for additional consultations/explorations, laboratory results or hospital readmission during the study follow-up period were also collected.

Patients and study size, including dropouts

The sample size was calculated based on the primary evaluation criteria, the incidence of nephrotoxicity. The expected incidence of nephrotoxicity was estimated based on results reported in the literature with a high dose of vancomycin (Ctrough ≥15 mg/L) as historical reference. According to previous studies (presented in Table 30, Annex 4), the incidence of nephrotoxicity associated with a high dose of vancomycin (Ctrough ≥15 mg/L) varied between 6.90% and 55.1%. Meta-analysis using random effects models estimated the incidence of nephrotoxicity associated with a high dose of vancomycin to be about 22%.

The primary analysis was descriptive and including 300 patients should ensure an acceptable precision (half-length of 95% CI) of 5% to describe expected incidence of 22%.

In addition, the inclusion of 300 patients should allow evaluating if the incidence of nephrotoxicity with teicoplanin would not exceed vancomycin's historical reference incidence by more than 5% (considered as the non-inferiority [NI] margin).

The upper boundary associated with the 95% two-sided confidence interval of the observed incidence should be <27% (ie, historical reference incidence + NI margin: 22+5), to evaluate non-inferiority versus vancomycin. Assuming a slightly better true incidence of 20% under teicoplanin, a sample size of 300 patients would provide 80% power to evaluate the non-inferiority.

Variables and data sources

- Data management, review, validation: Data entry in the eCRF needed to be performed by investigational centers within a 5-day window relative to each planned study visit in the protocol. Completion guidelines provided instructions to centers on how to report information in the eCRF. Regarding the data validation, the specifications of the automatic checks applied on the data were defined in the Data Validation Plan (DVP) including validation listings used for manual review from which Data Resolution Forms (DRF) might be edited manually. Checks and listings were validated in testing environment before use in production environment.
- Statistical considerations:
- The safety population consisted of eligible patients who signed the ICF and were exposed to at least one dose of teicoplanin
- The high dose treated population consisted of eligible patients who signed the ICF and were exposed to at least one high loading dose of teicoplanin
- The modified high dose treated population consisted of eligible patients who signed the ICF and were exposed to ≥3 high loading doses of teicoplanin, with at least 2 injections within 24 hours, a first dose >10 mg/kg and a cumulative dose ≥20 mg/kg within 30 hours. This population was the primary analysis population.

The analysis exposure to teicoplanin was divided into two analysis periods:

- Loading dose analysis period (from the first teicoplanin administration up to Day 10)
- Maintenance dose analysis period (from Day 11 until the last administration).

Premature withdrawals from the study before Day 10 were considered in the loading dose analysis period.

- Variables and evaluation criteria:
  - The primary evaluation criteria consisted of nephrotoxicity defined as increase in serum creatinine more than 0.5 mg/dL if the baseline serum creatinine was ≤3 mg/dL, or a rise of >1 mg/dL if the initial serum creatinine was >3 mg/dL, or 50% increase from baseline, or a drop in calculated creatinine clearance using Cockroft-Gault formula of ≥50% from baseline, reported in association with teicoplanin over the loading dose analysis period (up to Day 10). All nephrotoxicities were to be reported as adverse events (AE) as well. Any cases of potential nephrotoxicity were reviewed by the Independent Clinical Adjudication Committee (ICAC). Confirmed nephrotoxicity following this review was considered for the primary evaluation criteria. Signs of nephrotoxicity classified as non-assessable by the ICAC were considered as missing data and therefore were not taken into account in percentages calculation (cases considered by the ICAC as non-assessable included cases with extra-renal treatment before the start of teicoplanin (ie, one patient with renal replacement therapy via Continuous Venous-Venous Hemo Dia Filtration (CVVHDF)), difficult multi-infection context, or insufficient clinical documentation).
- The secondary evaluation criteria were:
  - Incidence of nephrotoxicity during the maintenance dose analysis period and the global study period, as defined like for the primary evaluation criteria
  - Incidence of nephrotoxicity during the loading dose analysis period, the maintenance dose analysis period and the global study period, as identified thanks to the Medical Dictionary for Regulatory Activities (MedDRA) coding of adverse events, from the SMQs 20000003 “Acute renal failure”, 20000213 “Chronic kidney disease”, and 20000220 “Proteinuria” (Broad and Narrow)
  - Incidence of hepatotoxicity during the loading dose analysis period, the maintenance dose analysis period and during the global study period. Hepatotoxicity was defined as: aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3 times upper limit of normal (when AST or ALT was normal or missing at baseline) or, if AST or ALT baseline was abnormal, AST or ALT increase of ≥ 3 times the baseline; and/or adverse events/reactions using the MedDRA SMQ “Hepatic Disorders”
  - Incidence of thrombocytopenia (platelets <100 000/mm3 or <100 Giga/L) during the loading dose analysis period, the maintenance dose analysis period and during the global study period.
  - Incidence of Hearing and balance/vestibular disorders, identified thanks to the MedDRA coding of adverse events, from the Hearing and vestibular disorders SMQ 20000170 (narrow) and additionally the PT “Balance disorder”, during the loading dose analysis period, the maintenance dose analysis period and during the global study period
  - Additional renal endpoints such as renal failure, dialysis and renal replacement therapy were included during the loading dose analysis period, the maintenance dose analysis period and during the global study period
  - Any adverse event/reaction during the loading dose analysis period, the maintenance dose analysis period and during the global study period.

- Data analyses: The primary analysis was descriptive and the incidence of nephrotoxicity over the loading dose analysis period (up to Day 10) was computed with exact binomial 95% confidence interval (CI). Multiple occurrences of nephrotoxicity in the same patient were counted only once. In addition, evaluations versus external historical reference (high dose of vancomycin) and versus lower loading dose of teicoplanin were performed:
  - Evaluations versus external historical data for nephrotoxicity associated with high dose of vancomycin: Observed results versus historical reference incidence of 22% (incidence associated with the high dose of vancomycin) was evaluated and discussed regarding the upper boundary associated with confidence interval of the observed incidence (an upper boundary <27%; historical reference incidence + NI margin: 22+5).
  - Evaluations versus external historical data for nephrotoxicity associated with lower loading dose of teicoplanin (6 mg/kg BID): Observed results versus historical reference incidence of 2% (incidence associated with the lower loading dose of teicoplanin) was evaluated and discussed regarding the boundaries associated with confidence interval of the observed incidence.
- Secondary analyses were mainly descriptive and consisted also in incidence rates and associated 95% CI.
- Other endpoints were analyzed with descriptive analyses and by time to event analyses.
- In addition, exploratory statistical analyses were performed to evaluate the influence of baseline covariates (age, gender, body mass index, creatinine clearance, concomitant medications, comorbidities [predefined list of pathologies proposed in the electronic case report form], type of infection [infective endocarditis, bone and joint infection, or other severe infection],and other covariates [teicoplanin number of high loading doses, trough teicoplanin serum concentration assessed by FPIA, HPLC or other method, overdose*, indication of HLD teicoplanin for other severe infections and route of administration of teicoplanin different from IV or IM]) on the development of nephrotoxicity, hepatotoxicity, thrombocytopenia, hearing and balance/vestibular disorders, by use of logistic regression models.
  *"Overdose" was defined as subjects with at least one adverse event overdose reported; and/or having received 6 high loading doses (HLD) or more; and/or having received at least one dose >13mg/kg.
- The final analysis presented data collected for the 300 included patients. Data collection started on 21 Apr 2016. The database lock was performed on 17 July 2019.

Results

- Overall participation status:

Table 1 - Abstract - Overall participation status

	Participating centers*	Patients enrolled	Patients treated
France	12	141	141
Germany	2	12	12
Italy	4	20	20
Poland	2	9	9
Romania	4	12	12
United-Kingdom	8	106	106
Total	32	300	300

* participating centers: Sites who enrolled at least one patient
Source: Annex 2 statistical results Table 1-1-2, Table 1-2-1

- Participation per period of the study and per analysis population:

Table 2 - Abstract - Participation per period of the study

Country	Number of enrolled patients*	Number (%) of patients in Safety population **	Number (%) of Patients in the High Dose Treated Population +	Number (%) of Patients in the Modified High Dose Treated Population ++	Number (%) of Patients with Maintenance dose period initiated	Number (%) of patients with teicoplanin treatment completed as planned
All	300	300 (100.0%)	296 (98.7%)	287 (95.7%)	202 (67.3%)	205 (68.3%)
France	141	141 (100.0%)	140 (99.3%)	136 (96.5%)	111 (78.7%)	99 (70.2%)
Germany	12	12 (100.0%)	12 (100.0%)	12 (100.0%)	3 (25.0%)	7 (58.3%)
Italy	20	20 (100.0%)	19 (95.0%)	19 (95.0%)	17 (85.0%)	14 (70.0%)
Poland	9	9 (100.0%)	9 (100.0%)	9 (100.0%)	4 (44.4%)	4 (44.4%)
Romania	12	12 (100.0%)	11 (91.7%)	11 (91.7%)	6 (50.0%)	10 (83.3%)
UK	106	106 (100.0%)	105 (99.1%)	100 (94.3%)	61 (57.5%)	71 (67.0%)

* Enrolled patients: All patients who signed ICF
** Safety population: eligible patients who signed the ICF and received at least one dose of teicoplanin
+ High dose treated population: Eligible patients who signed the ICF and received at least one high loading dose of teicoplanin.
++ Modified high dose treated population: Eligible patients who signed the ICF and received >=3 administrations of the high loading dose of teicoplanin.
% are computed on the enrolled patients
Source: Annex 2 statistical results Table 1-2-1, Table 1-2-2

- Descriptive data: Population characteristics
  - Three hundred (300) patients with a mean (SD) age of 63.1 (15.0) years were enrolled in the study; they were mostly male (205, 68.3%).
  - Most patients (183, 61.0%) were treated with teicoplanin for a bone and joint infection, 12.3% (37) for an infective endocarditis and 26.7% (80) for other indications (other severe infection).
  - Two hundred and five (205, 68.3%) patients completed teicoplanin treatment as planned. Ninety-five (95, 31.7%) patients did not complete teicoplanin treatment as planned: 46 (15.3%) discontinued because of adverse events, 16 (5.3%) because of lack of efficacy and 33 (11.0%) for other reasons.
  - The median duration of treatment with teicoplanin in the entire treatment period was 16.0 days. During the high loading analysis period, a total of 165 patients (55.6%) received 3, 4 or 5 HLD; a total of 49 patients (16.5%) received 6 HLD, 24 patients (8.1%) received 7 HLD, 24 patients (8.1%) received 8 HLD and 25 patients (8.4%) received 9 HLD or more.
- Safety results
  - In the Safety Population, a total of 164 (54.7%) patients had an "overdose" of teicoplanin, "overdose" being defined as: subjects with at least one adverse event overdose reported; and/or having received 6 HLD or more; and/or having received >=1 dose > 13 mg/kg.
- Nephrotoxicity:
  - Primary endpoint: during the loading dose analysis period, in the modified High-dose treated population (N=287), 28 patients presented a nephrotoxicity confirmed by ICAC. The corresponding percentage was 11.0% [7.4%; 15.5%]. With an upper limit of the 95% CI of 15.5%, this is therefore < 27% (the non-inferiority margin versus vancomycin). This was also true in the Safety and High-dose treated analyses populations, as well as for both sensitivity analyses (missing data considered as half of the observed frequency, and missing data considered as twice the observed frequency).
    The 95% CI was [7.4%; 15.5%] during the high loading dose analysis period, in the modified High-dose treated population, therefore > 2% (the incidence associated with the lower loading dose of teicoplanin).
  - Secondary endpoint: The percentage of patients with nephrotoxicity validated by ICAC ranged from 6.7% to 6.9% during the maintenance dose analysis period and from 20.6% to 20.9% during the complete study period (depending on the analysis populations).
- Hepatotoxicity: the percentage of patients with hepatotoxicity ranged from 8.5% to 8.8% during the loading dose analysis period, from 7.6% to 7.9% during the maintenance dose analysis period and from 12.7% to 12.9% during the complete study period (depending on the analysis populations).
- Thrombocytopenia: the percentage of patients with thrombocytopenia ranged from 6.9% to 7.4% during the loading dose analysis period, from 3.8% to 4.0% during the maintenance dose analysis period and from 11.4% to 12.3% during the complete study period (depending on the analysis populations).

- Hearing and balance/vestibular disorders: the percentage of patients with at least one AE related to hearing and balance/vestibular disorder was 0.7% during the loading dose analysis period, 1.5% during the maintenance dose analysis period and ranged from 2.0% to 2.1% during the complete study period (depending on the analysis populations).
- Potential predictive factors identified from the exploratory and informative multivariate analysis for nephrotoxicity were the cumulative doses of HLD, prior peripheral vascular disorder (ongoing or not at baseline) and the value of the creatinine clearance at baseline (lower value linked with a higher risk).
- Potential predictive factors for hepatotoxicity were the body mass index (lower risk if higher body mass index), hypotension and liver disorder (all prior, ongoing or not at baseline).
- Potential predictive factors for thrombocytopenia were history of hypovolemic shock, liver disorder, chronic kidney disease and hematological malignancy (all prior, ongoing or not at baseline).
- No potential predictive factor was found for hearing and balance/vestibular disorders.
- Interpretation of these results should be conducted very cautiously, as the type of study and the number of evaluable patients does not allow establishing causal associations between covariates and occurrence of nephrotoxicity, hepatotoxicity and thrombocytopenia with sufficient power.
- In the Safety Population, during the complete study period, 235 (78.3%) patients presented at least one TEAE (whatever relationship to teicoplanin), 96 (32.0%) presented at least one TEAE related to teicoplanin according to the investigator, 124 (41.3%) presented at least one SAE (including 19 (6.3%) who presented at least one SAE related to teicoplanin according to the investigator), 31 (10.3%) patients died (including one patient with death assessed as related to teicoplanin according to the investigator). Amongst the 31 patients who died, 10 belonged to the group of the 183 patients treated with teicoplanin for a bone and joint infection (10/183, 5.5%), 7 belonged to the group of the 37 patients treated for infective endocarditis (7/37, 18.9%), and 14 belonged to the group of the 80 patients treated for another severe infection (14/80, 17.5%). A total of 37 patients (12.3%) presented one TEAE leading to withdrawal of treatment with teicoplanin.
- Pharmacokinetic results:
  - For the loading dose analysis period (Day 1-10), pharmacokinetic results were considered evaluable and analyzed when the sample was collected [6h to 24h] after the previous dose of teicoplanin. Only 158 patients (53%) had at least one evaluable sample during the loading dose analysis period.
  - For the maintenance dose analysis period, pharmacokinetic results were considered evaluable and analyzed when the sample was collected [12h to 48h] after the previous dose of teicoplanin. Only 95 patients (47% of patients in the maintenance dose analysis period) had at least one evaluable sample during the maintenance dose analysis period.

- Overall (ie, in all patients with assessable sampling), the mean (SD) teicoplanin serum trough concentration (assessed by FPIA, HPLC or other method) during the loading dose analysis period was 28.18 (9.40) mg/L ; the mean (SD) teicoplanin serum trough concentration was 32.85 (9.97) mg/L in patients with nephrotoxicity confirmed by ICAC during the loading dose analysis period, and 27.88 (9.26) mg/L in patients without nephrotoxicity confirmed by ICAC).

Discussion

The analysis of the complete set of the 300 patients included in this PASS (OBS13842-POSY-TEICO) confirmed the inclusion of a representative sample of patients treated with high loading dose of teicoplanin in real-life setting, in terms of demography, disease characteristics and associated comorbidities.

The rate of patients with nephrotoxicities confirmed by the ICAC was 11.0% [7.4%; 15.5%] during the loading dose analysis period in the primary analysis population (modified High-dose treated population). The upper limit of the 95% CI was 15.5%, i.e. <27%, thus indicating non-inferiority margin versus vancomycin (presented in Table 30, Annex 4). Results were consistent also in the safety and high dose treated analyses populations, and for both sensitivity analyses (missing data considered as half of the observed frequency, and missing data considered as twice the observed frequency).

The rates of patients with hepatotoxicity, thrombocytopenia, hearing and balance/vestibular disorders, additional renal endpoints and any adverse events does not raise concern for this population of patients with severe infections, treated by high loading doses of teicoplanin.

Conclusion

Loading doses of teicoplanin of 6 mg/kg BID for 3 administrations is recommended for most infections, and 12 mg/kg BID for 3 to 5 administrations should be considered for severe infections such as endocarditis and bone and joint infections.

The primary objective of the study was to determine the incidence of nephrotoxicity reported in association with teicoplanin higher loading doses of 12 mg/kg twice a day, over the loading dose analysis period (up to Day 10).

During the high loading dose analysis period, in the modified High-dose treated population, 28 patients presented a nephrotoxicity confirmed by ICAC. The corresponding percentage was 11.0% [7.4% to 15.5%]. The upper limit of the 95% CI was 15.5%, therefore <27% (non-inferiority margin versus vancomycin from historical data). This was also true in the safety and high dose treated analyses populations, as well as for both sensitivity analyses.

For the whole study period, the rate of nephrotoxicity was 27.6% for patients with overdose versus 11.9% for other patients (no overdose), 21.2% for patients with teicoplanin HLD used for infectious endocarditis or bone and joint infection versus 18.9% for other patients, and 28.6% for patients with SC route administration used versus 19.2% for other patients (teicoplanin administered with IM or IV route).

The percentage of patients with nephrotoxicity confirmed by ICAC ranged from 6.7% to 6.9% during the maintenance period and from 20.6% to 20.9% during the complete study period (depending on the analysis populations).

The percentage of patients with hepatotoxicity ranged from 8.5% to 8.8% during the loading dose analysis period, from 7.6% to 7.9% during the maintenance period and from 12.7% to 12.9% during the complete study period (depending on the analysis populations).

The percentage of patients with thrombocytopenia ranged from 6.9% to 7.4% during the loading dose analysis period, from 3.8% to 4.0% during the maintenance period and from 11.4% to 12.3% during the complete study period (depending on the analysis populations).

The percentage of patients with at least one AE related to hearing and balance/vestibular disorder was 0.7% during the loading dose analysis period, 1.5% during the maintenance period and ranged from 2.0% to 2.1% during the complete study period (depending on the analysis populations)..

Overall, the data in this study suggests that the safety profile of teicoplanin when used as per the newly approved dosing regimen in patients with infective endocarditis or with severe bone or joint infection is favorable.

Marketing Authorization Holder(s)

Sanofi-aventis

Study Personnel

The ICAC representative and Company responsible medical officer's signed approvals of the report are provided in Annex 2.

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The Company Internal Staff

The Company was responsible for providing adequate resources to ensure the proper conduct of the study.

The Company was responsible for local submission(s) complying with data protection rules and any other local submission(s) required.

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Not applicable.