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THERAPEUTIC GOODS ADMINISTRATION - AUSTRALIA
PRECLINICAL EVALUATION OF REGISTRATION APPLICATION

APPLICANT:	Marion Merrell Dow Ltd
DRUG NAME:	Teicoplanin
TRADE NAME:	Targocid
DOSE STRENGTH/FORM:	100, 200 and 400 mg powder for injection
EVALUATOR:	[redacted]
APPLICATION NO:	91-156-2
FILE NOs:	91/10911; 93/11783

This evaluation has been checked for confidential material and is cleared for release to the sponsor provided that pages 1, 17 and 53 are substituted with the attached pages.

SUMMARY:

1. Marion Merrell Dow Ltd have applied to register the glycopeptide antibiotic teicoplanin for IM and IV use in the treatment of a number of infections involving gram-positive bacteria (for example, endocarditis, septicaemia, osteomyelitis, peritonitis and infections of the urinary tract and soft tissues), and in surgical patients. The proposed dosage is 400 mg (about 6 mg/kg) on day 1, and 200 mg/kg/day (about 3 mg/kg/day) or 400 mg/day thereafter, possibly for up to 3 weeks.

A detailed preclinical evaluation for teicoplanin was prepared by [redacted] in 1986 for a clinical trial application (approved in May 1987). For the current application, the sponsor has submitted a further reproductive toxicity study, and evaluation of this is incorporated into the previous clinical trial evaluation.

2. Teicoplanin is chemically related to the vancomycin-ristocetin group of antibiotics. It has both bactericidal and bacteriostatic activity, with the bacteriostatic mechanism of action being similar to that of vancomycin.

Teicoplanin is active *in vitro* against aerobic and anaerobic gram-positive bacteria, including methicillin-resistant Staphylococci, Group D Streptococci, Clostridium difficile and group JK corynebacteria. Very weak or no activity was shown against gram-negative bacteria.

The *in vitro* activity of teicoplanin was supported by studies *in vivo* in mice (SC) and rabbits (IV), where teicoplanin was effective against infections due to susceptible organisms. In addition, teicoplanin combined with gentamicin was 2.5 times more effective than teicoplanin alone in the treatment of endocarditis in rabbits.

3. In the anaesthetised dog, an IV dose of 10 mg/kg teicoplanin resulted in slight but significant decreases in blood pressure, cardiac output and stroke volume. These changes were not observed in the conscious dog. Teicoplanin at doses > 3 mg/kg in mice and rats produced behavioural changes and, at 300 and 600 mg/kg, signs of CNS depression. Teicoplanin, at concentrations up to 5000 μg/mL *in vitro*, did not interfere with platelet function.

4. Pharmacokinetics studies were conducted in rats, mice and dogs. In general, teicoplanin is very poorly absorbed following oral ingestion in all species studied. Pharmacokinetic data for teicoplanin and/or active metabolites (determined by microbiological assay) after an IV dose are shown in the table.

Species	Dose mg/kg	C0 μg eq/mL	T½ h	AUC μg eq.h/mL	C24 h μg eq/mL
Rat IV	20	256-343	22	758-950	4.4-5.1
Dog IV	5	70	27	822	9
Human IV	6	112	44	521	4.2

The volume of distribution (approx. 0.4 L/kg in animals, 0.75 L/kg in humans) was consistent with diffusion into most liquid compartments. Teicoplanin is distributed to most tissues, with highest levels found in the kidneys, liver, adrenals and spleen in the rat. Metabolism studies were not conducted. However, data in the rat suggests that teicoplanin is not extensively metabolised and, after parenteral administration, is excreted mostly unchanged mainly in the urine. Excretion in the faeces accounted for about 15% of an IM dose over 4 days in rats.

5. The IV LD_{50} of teicoplanin was 106 mg/kg in rats, 750 mg/kg in dogs and 715 mg/kg in mice. Clinical signs were sedation, ptosis, dyspnoea, loss of weight, piloerection and injection site ulceration in all species, and, additionally, muscular tremors, ataxia, anorexia, salivation, and vomiting in dogs.

Evidence of liver and kidney damage (changes in tissue colour and increased organ size) was found in rats after a single IP dose of ≥ 250 mg/kg, and in dogs after a single IV or IM dose of ≥ 600 mg/kg. Histology revealed necrosis of the epithelia of the cortical renal tubules.

6. Tissue damage at the site of injection was observed in a number of local tolerance studies after IV, IM and SC administration of teicoplanin. The effects were dependent on dose, frequency of treatment and (to some extent) vehicle.

7. Consistent findings in repeat dose toxicity studies in rats and dogs were reductions in body weight, clinical signs (as for acute toxicity), reduced WBC counts after SC administration, reduced RBC parameters after IV administration, reduced total plasma proteins, and urinalysis findings suggestive of kidney damage.

The kidney was identified as the primary target organ for the toxic effects of teicoplanin, but drug-related changes (mainly increases in organ size) was also observed in the adrenals, spleen, pancreas and liver. Histopathological lesions were found in the kidneys (nephritis/nephrosis), tissues associated with the injection site, and pancreas. No renal toxicity was found at doses ≤ 25 mg/kg/day SC if treatment was for 8 days. A no effect dose in dogs was 20 mg/kg/day IV or IM for 1 month or 10 mg/kg/day for 6 months IM.

Organ degenerative changes and changes to blood chemistry after 6 months of treatment with teicoplanin (3-30 mg/kg SC in rats; 10-40 mg/kg IM in dogs) either reverted to normal or showed signs of reversal at the end of 9-10 week recovery periods.

8. Teicoplanin did not appear to have an ototoxic effect in the guinea pig, and was not associated with ophthalmological changes.

9. Teicoplanin did not increase the mutation rate in the Salmonella typhimurium histidine reversion test, saccharomyces cerevisiae, or schizosaccharomyces pombe. There were no clastogenic tests, and no carcinogenicity studies have been submitted.

10. Reproductive toxicity studies in rats found that teicoplanin was associated with an increase in the number of stillborn pups at doses $\geq$ 40 mg/kg (significant at 100 and 200 mg/kg/day), and an increase in mortality among sucklings during the first 4 days after delivery at 200 mg/kg. Mean pup weight was reduced by about 10% at doses $\geq$ 10 mg/kg/day in a peri- and post-natal study (treatment from day 15 of gestation to day 21 post partum). There were no effects on male and female fertility, pregnancy parameters, fetal parameters to day 21 of gestation, or pup development in rats at doses up to 200 mg/kg.

Pregnant rabbits were more sensitive than rats to the toxic effects of teicoplanin, with a high rate of mortality and spontaneous abortions occurring at 25 mg/kg SC in rabbits. There were no adverse effects at doses $\leq$ 15 mg/kg/day.

There was no evidence for teratogenic activity at doses up to 200 mg/kg in rats, and 15 mg/kg in rabbits. However, teicoplanin was maternotoxic at doses $\geq$ 100 mg/kg in rats and $\geq$ 25 mg/kg in rabbits.

ASSESSMENT

Pharmacology

Teicoplanin demonstrated potent antibacterial activity against a number of clinically relevant organisms in both in vitro and in vivo studies. MIC_{90} values of about 0.1-0.4 μg/mL were obtained against Staphylococci aureus and epidermidis, and Streptococci pyogenes, pneumoniae and faecalis. These MIC90 values for teicoplanin are lower than trough plasma levels expected in humans after a dose of 200 mg/kg IV or IM (about 2 μg eq/mL). Furthermore, organisms susceptible to teicoplanin are involved in the infections for which teicoplanin is proposed to be indicated, but some of the organisms involved in the infections are not susceptible to teicoplanin.

The activity of teicoplanin was generally greater than or equal to that of vancomycin and other reference antibiotics against all these organisms except Streptococcus pyogenes, where all other antibiotics (except vancomycin) were more effective. The in vitro activity of teicoplanin was confirmed in in vivo studies, where teicoplanin was effective in the treatment of mice infected with Streptococcus pyogenes, Streptococcus pneumoniae and

Staphylococcus aureus. In addition, teicoplanin was as effective as reference antibiotics in the treatment of endocarditis induced in rabbits by methicillin-resistant and methicillin-sensitive strains of Staphylococcus aureus, Staphylococcus epidermidis or Streptococcus faecalis. These studies support a physiologically relevant role for teicoplanin in the treatment of infections due to susceptible organisms.

Teicoplanin displayed very weak activity (MIC 10-20 μg/mL) against Proteus vulgaris and E. coli, and virtually no activity (MIC about 100 mg/mL) against a number of other gram-negative bacteria.

<u>Secondary pharmacology</u>

Limited secondary pharmacology studies were conducted. Teicoplanin administered parenterally to normotensive conscious dogs had no cardiovascular effects at doses up to 60 mg/kg/day. However, mean arterial blood pressure, cardiac output and stroke volume were reduced at 10 mg/kg in anaesthetised dogs, suggesting that the drug may alter cardiovascular functioning under conditions where normal homeostatic mechanisms are altered. CNS effects were observed in rats and mice at IP doses greater than 3 mg/kg (exact doses unclear), and CNS depression was seen at IP doses of 300 mg/kg or greater.

Signs suggesting CNS depression (sedation, ptosis, ataxia, dyspnoea) were also seen in the acute toxicity studies, and in some of the repeat dose toxicity studies in dogs. In the repeat dose studies, many of the signs were reduced in severity or absent after repeated administration. The mechanism by which these effects occur, and whether the effects are due to direct actions on the CNS or due to changes in the activity of peripheral organs (eg, the adrenal glands), is not known.

<u>Pharmacokinetics</u>

There were a number of deficiencies in the pharmacokinetic data for teicoplanin. In most of the studies (human and preclinical), a microbiological assay was used to determine levels of teicoplanin and (unidentified) active compounds. However, the development of an assay which measured teicoplanin levels specifically, as well as methods to identify and quantitate any metabolites, would have been preferable. Similarly, the method used for the biosynthesis of [^{14}C]-teicoplanin (fermentation of [^{14}C]-glucose by <u>Actinoplanes</u> <u>teichomyceticus</u>) was not considered acceptable since there was no direct evidence that [^{14}C]-teicoplanin had been produced, since the nature of the labelled compound/s was not identified. In addition, recovery of the administered radioactivity was poor in many in the studies, but the reasons for this were not apparent or investigated. It is presumed that the remaining radioactivity was largely still in the carcass.

The major pharmacokinetic studies were single dose studies in rats by the IV, IM and oral routes, and in dogs by the IV and IM routes of administration. However, the major toxicity studies in rats were conducted by the SC route of administration, for which there was no data. In addition, apart from 24 h plasma drug levels in the repeat dose studies, pharmacokinetic studies after multiple doses were not conducted. Although there was substantial plasma kinetics data, studies on the metabolism, distribution and excretion of teicoplanin and related compounds were either absent (metabolic studies in particular) or deficient. Because of this, it was difficult to assess the suitability of the rat and dog for use in the toxicity studies based on pharmacokinetic comparisons between animals and humans.

It should also be noted that the relevance of the maternotoxicity in rabbits (identified in reproductive toxicity studies), was difficult to assess because of the absence of pharmacokinetic data for this species.

The main findings from the single dose pharmacokinetic studies are given in the table:

Species	**Dose mg/kg**	**C0/Cmax μg eq/mL**	**T½ h**	**AUC μg eq.h/mL**	**C24 h μg eq/mL**
Mouse SC	5	2	2.5	58	-
Rat IV	20	256-343	22	758-950	4.4-5.1
Rat IM	20	8.8	32	442	7.21
Dog IV	5	70	27	822	9
Dog IV	40	565	28	6001	66
Dog IM	5	21	30	742	8
Human IV	3	54	47	256	2.1
Human IV	6	112	44	521	4.2
Human IM	3	7	48	231	2.3

Tmax after IM administration was at 8 h in the rat and dog (2 h if teicoplanin was dissolved in povidone rather than saline in dogs) but 2 h in humans (saline formulation). Pharmacokinetics were linear over 5-10 mg/kg SC in mice, 5-40 mg/kg IV in dogs, and 3-6 mg/kg IV in humans.

Approximate values for clearance (mL/h/kg) were 8 in dogs, 5 in rats and 9 in humans. Approximate values for volume of distribution (L/kg) were 0.35 in dogs, 0.7 in rats and 0.8 in humans, which was consistent with the drug being distributed predominately in body water.

In rats, plasma levels of teicoplanin and/or related compound were about 25-30% lower in males than in females after IV (and most likely after SC) dosing, but the IV half life of the drug was similar in both sexes. The sponsor attributed this difference to the smaller V_D in females (0.69 L/kg in females compared with 0.85 L/Kg in males after IV dosing).

Tissue distribution studies were conducted only in male rats after IM administration of [^{14}C]-teicoplanin and in female rats after oral administration of [^{14}C]-teicoplanin. In male rats, highest levels of radioactivity in tissues relative to levels in plasma were found in the kidneys, adrenals, liver, intestine, femur and spleen. The relative concentrations of radioactivity in these tissues were consistently high from 6-48 h after drug administration, and increased over time: at 48 h, the tissue:plasma ratio was about 24 in the kidneys, 20 in the adrenals, 15 in the liver, 14 in the femur and 5 in the spleen. These findings are of some significance since the kidney, adrenals, liver and spleen were the main organs with drug-induced damage in the repeat dose toxicity studies.

Drug retention at the injection site after IM administration in rats appears to be substantial: about 21% of the dose remained in the injected leg 24 h after dosing, and about 10% remained at 4 days after dosing.

It is possible that teicoplanin is absorbed across the blood brain barrier since CNS depression was found in the secondary pharmacology studies, and clinical signs suggesting effects on the CNS were seen in the acute and repeat dose toxicity studies. However, there was no direct evidence for this, and very little drug was found in the CSF after administration to humans.

The excretion of teicoplanin and/or related compounds was investigated in the rat and dog. It is likely that, after parenteral administration, teicoplanin and/or metabolites (if any) are excreted predominately in the urine in both species. In rats, about 50% of the dose was recovered in urine 24 h after an IV dose or 4 days after an IM dose. About 15% of the IM dose in rats was recovered in faeces over 4 days. Urinary excretion over 5 days also accounted for about 50% of an IV dose and 65% of an IM dose in dogs, but faecal excretion in this species was not investigated. No evidence for biliary excretion was found in a preliminary experiment in one dog. However, this was an indirect study which measured plasma levels of teicoplanin and related compounds during intact and interrupted biliary function, therefore no conclusions can be made from this.

After an oral dose of teicoplanin in rats, about 1% of the dose was recovered in bile over 4 h, and > 95% is recovered in faeces over 7 days, which is consistent with very poor oral absorption of teicoplanin.

The metabolic breakdown of teicoplanin was not investigated in animals. However, in the rat, it was found that measurement of urinary excreted compounds by liquid scintillation counting (parent plus all related compounds) or by microbiological assay (parent plus active compounds) was almost identical, suggesting that the drug is excreted predominately unchanged and/or as active metabolites. A somewhat inconsistent finding was that about 30-70% of the drug-related compounds in plasma were inactive metabolites of teicoplanin. However, the inconsistency in the findings was probably due to technical rather than physiological reasons.

Acute toxicity

The IV acute toxicity of teicoplanin was greatest in rats (LD_{50} of 106 mg/kg), and similar in dogs and mice (715-750 mg/kg). The LD_{50} values after IP or SC administration were 2-32 times higher compared with the IV LD_{50}, probably because bioavailability after SC or IP administration is < 100%. The oral acute toxicity of teicoplanin in rats and mice (LD_{50} > 10,000 mg/kg) is probably negligible.

Clinical signs of acute toxicity were similar in rats, mice and dogs, and several (sedation, ptosis, dyspnoea) appeared to indicate CNS depression. Additional signs in these species were local irritation, anorexia, vomiting, weight loss, muscle tremors and ataxia. Renal damage (as seen in repeat dose toxicity studies; see below) was evident in all species after a single dose of ≥ 250 mg/kg IP in rats and ≥ 600 mg/kg IV or IM in dogs.

<u>Local tolerance</u>

Local tolerance studies in dogs, rats and rabbits (IV, IP and IM) found that teicoplanin in various vehicles (including saline - proposed for registration) has potential to cause irritation and tissue damage at the site of injection after either single or multiple administrations. Local inflammation and tissue damage were seen after low doses and single administrations, but the severity of the effects was dependent on dose, frequency of administration and vehicle. The nature of the lesions was similar in all species, but investigations of the reversibility of the effects were not (apparently) investigated in any study.

Local toxicity after IV administration consisted of phlebitis, periphlebitis and proliferation of connective tissue around the target vein. Additionally, subcutaneous haemorrhagic suffusions were found after long term IV administration. These effects were not seen in IM and SC studies, where lesions where characterised by alopecia, skin thickening, eschars/scabs, inflammation, hyperaemia and bleeding. Additional lesions after IM administration consisted of focal necrosis and degenerative changes in the muscle fibres, echymoses and oedema. Dogs also often showed signs of pain and lameness of the leg used for injection.

These findings demonstrated that teicoplanin has potential to cause irritation and tissue damage at the site of injection after either a single or repeated injections at low as well as high doses. This suggests that the site of injection for repeated clinical administration of teicoplanin may need to be varied.

<u>Repeat dose toxicity</u>

Several repeat dose toxicity studies were conducted using teicoplanin administered parenterally for 1 and 6 months in rats and dogs. All were conducted at G. Lepetit laboratories between 1980-1984, and were stated to have complied with GLP.
One month studies were conducted in rats using doses of 10, 20, 40 and 80 mg/kg/day IV, 25, 50, 100 and 150 mg/kg/day SC and 10, 20, 50 and 150 mg/kg/day SC, and in dogs using doses of 5, 10, 20 and 40 mg/kg/day IV and IM. Compared to events after IV dosing, the development of clinical signs and toxicity were slightly less severe after SC administration in rats, and markedly less severe after IM administration in dogs.

Six months treatment, 9-10 weeks recovery studies using lower doses of teicoplanin (5, 10 and 30 mg/kg/day SC) in rats and doses of 10, 20 and 40 mg/kg/day IM in dogs were also conducted.

An 8 week study comparing the effects of teicoplanin (25, 50 and 100 mg/kg/day) with those of vancomycin (100 and 500 mg/kg/day) was also conducted.

It should be noted that dose ranging studies were not conducted and that toxic effects in all of the dog studies were generally mild. Doses used in rats were sufficient. Toxicities identified in the 6 month studies in rats and dogs were reversible over 9-10 weeks.

Findings in the toxicity studies are outlined below:

Mortality, clinical signs and body weight

Mortalities in the rat studies were not clearly related to treatment with teicoplanin since they did not always occur at the higher doses, and were not seen consistently across the studies. Furthermore, autopsies were not carried out. There were no mortalities in the dog studies.

Clinical signs in the 1 month studies in rats were similar to those seen in the acute toxicity studies (reduced spontaneous activity, dyspnoea, and ataxia), occurred at all doses, increased in severity with dose. However, after 10 days of treatment, clinical signs were absent at lower doses (10 and 20 mg/kg) and reduced in severity at the higher doses, suggesting some form of tolerance had occurred with repeated treatments. These signs were not seen in the 6 month rat study, but irritation and tissue damage at the site of injection were seen at all dose levels in the 1 and 6 month studies.

No clinical signs were reported in the 1 month IV study in dogs, and only local irritation was seen in the 1 month IM study. However, in the 6 month study, signs similar to those found in the acute toxicity studies (sedation, vomiting and muscle tremors) were observed in various dosage groups and at various times during the study. Lameness was also reported.

In the 1 month rat studies, reductions in body weight (about 10-15%), which persisted throughout treatment, were seen with 80 mg/kg IV and ≥ 100 mg/kg/day SC, and were associated with reduced food consumption only in SC treated animals. Body weight was also reduced after 8 weeks of treatment with lower doses (10 and 30 mg/kg) in rats, and this either reversed (males) or persisted (females) at 8-9 weeks after treatment ceased. There were no effects on body weight in any of the dog studies.

Urinalysis

Urinalysis in the 1 month rat and dog studies was consistent with evidence of renal damage (see below). Urine from rats treated with ≥ 40 mg/kg/day IV and ≥ 50 mg/kg/day SC, and dogs treated with 40 mg/kg/day IV (but not IM) often contained sloughed cells from the upper and lower urinary tract, granular casts, red blood cells and haemoglobin. Additionally, proteinuria and the presence of leukocytes in urine were found in rats treated with doses ≥ 100 mg/kg/day SC.

Urinalysis in the 6 month studies revealed only urinary casts at 30 mg/kg/day in rats, and at 20 and 40 mg/kg/day in dogs. These decreased in number after 3 months of treatment in rats, suggesting tolerance, and were absent after treatment ceased in either rats or dogs.

Haematology

Haematological changes were found only in rat studies: A 10% decrease in red blood cell parameters was found only in females treated with ≥ 10 mg/kg/day teicoplanin IV in the 1 month study, and in males and females treated with 30 mg/kg/day SC for at least 3 months in the 6 month study, but it is unclear if the effect was reversible. These changes were not seen in the 1 month SC study.

A dose-related decrease in white blood cell counts (up to 50-60% at 150 mg/kg in the 1 month study and 81% at 30 mg/kg in the 6 month study) was seen consistently in all rat SC studies at all dose levels. Associated decreases in lymphocytes and increases in neutrophils were also seen consistently. The effect on WBC was reversed once treatment was withdrawn in the 6 month study. It is possible that changes to WBC counts were associated with tissue damage at the site of injection, since they were not seen after IV administration of similar doses.

There were no haematological changes in the dog studies, but enlargement of the spleen was observed at 40 mg/kg/day in the 6 month study.

Clinical biochemistry

Consistent findings in rats were of reduced total proteins (maximum of about 20% at 150 mg/kg SC) at all dose levels in all studies. This effect was reversed in the 6 month study once treatment had ceased, and may be related to renal toxicity (see below), but proteinuria was seen only in HD SC treated rats. The reduction in total proteins was often accompanied by a shift in the albumin:globulin ratio, due mainly to reduced globulin and increased albumin levels. A shift in the albumin:globulin ratio was also seen in the 1 month IV study in dogs at 40 mg/kg, but no other changes to plasma proteins were reported.

Other consistent biochemical changes in rats were increases in BUN, increases in SGPT, and reductions in serum AP levels. These changes were marked at the highest dose in the 1 month SC study, but variable at the lower doses in the 6 month study where they did not persist once treatment was withdrawn. No changes to clinical chemistry outside of biological limits were found in the dog studies.

Organ weights and gross pathology

Pale kidneys, gross lesions at the injection site, and enlarged spleen were found consistently in all of the rat studies at all doses. In dogs, pale kidneys were seen in the 1 month IV (but not IM) study at 40 mg/kg, and in the 6 month study at all dose levels. Pale livers were also seen in dogs in the 1 month IV study at 40 mg/kg and in the 6 month study at 20 and 40 mg/kg. Enlargement of the spleen was seen at 40 mg/kg in the 6 month study only. These effects were reversed once treatment ceased.

Effects on organ weights in the 1 month rat studies were somewhat variable between individual studies and between males and females in the same study, particularly when relative and absolute weights were considered. This may be related partly to variable changes in body weight. However, in general in the 1 month rat studies, increases in the weight of the adrenals (at all doses; up to 38% (absolute) at high doses), kidneys (all doses; up to 47-75%), liver (all doses, but effect not dose-related), and spleen (mainly at doses ≥ 80 mg/kg; up to 50-70%) were found. The effects in the adrenals and liver were significant only in females. Increases in the weight of the kidneys, but not the liver, adrenals or spleen, were accompanied by histopathological changes to these organs (see below). Increases in the weight of the kidneys, liver and spleen were also found at 40 mg/kg in the 6 month study in dogs, but not in the 1 month studies.

Changes to organ weights in rats were compared after 3 and 6 months of treatment with lower doses. After 3 months of treatment at 5, 10 and 30 mg/kg/day, dose-related increases in the weight of the liver, kidneys, spleen, adrenals (females only) and gonads/uterus occurred. The increases in the liver and kidney of males reversed after 6 months of treatment, but changes in other organs persisted or increased, and an increase in adrenal weight in males was seen after 6 but not 3 months of treatment.

Histology

Histopathological changes were observed at the injection site, kidneys and pancreas in rats, and at the injection site, kidneys and liver in dogs.

Changes to the <u>kidneys</u> consisted of degeneration and/or necrosis of cortical tubular epithelia, and hyaline casts of proteinaceous material in the lumen of the tubules. Evidence for nephritis/nephrosis was found at doses ≥ 40 mg/kg/day IV or ≥ 50 mg/kg/day SC for 1 month in rats. In the 6 month study in rats, renal tubular dilatation (as well as pale kidneys, increases in renal weight and the appearance of granular casts in urine) was observed at doses ≥ 10 mg/kg/day. No adverse renal effects were seen at doses of 5 mg/kg/day for 6 months in rats. The dose, corresponding 24 h plasma drug level at steady state, and estimated AUC (from pharmacokinetics data) associated with renal toxicity in each study are given in the table:

Dose/day	Duration & Route	C24 h µg eq/mL	AUC µg eq.h/mL	Safety Margin** C24	AUC
Rat:					
40 mg/kg	1 month IV	5	774	1	1.5
50 mg/kg	8 days or 1 month SC	20	523*	5	1
10 mg/kg	6 month SC	6	221*	1.4	< 1
Dog:					
40 mg/kg	1 month IV	133	6001	32	12
20 mg/kg	1 month IM	63	2968	16	6
10 mg/kg	6 month IM	37	1484	9	3

* AUC according to data obtained after IM administration.
** The safety margin assumes a human IV dose of 6 mg/kg, which gives 24 h plasma levels of 4.2 µg eq/mL and AUC of

521 μg eq.h/mL. It should be noted that plasma levels in humans are after a single dose whereas steady state levels are given in animals. AUC values are for a single dose in humans and animals.

These calculations assume linear pharmacokinetics, and assume that bioavailability after an IM dose is the same as that after an SC dose. The safety margin therefore increases proportionally if bioavailability after SC administration is less than that after IM or IV administration in humans.

The following table shows the doses at which no renal toxicity was observed:

Dose/day	Duration & Route	C24 h μg eq/mL	AUC μg eq.h/mL	Safety Margin C24 h	Safety Margin AUC
Rat:					
20 mg/kg	1 month IV	3	850	< 1	1.6
20 mg/kg	8 days or 1 month SC	10	442*	2.4	< 1
5 mg/kg	6 month SC	2	111*	< 1	< 1
Dog:					
20 mg/kg	1 month IV	60	3000	14	6
10 mg/kg	1 month IM	37	1484	9	3
**	6 month IM	< 38		< 9	< 3

* AUC according to data obtained after IM administration.
** A no effect dose was not determined.

Thus, it appears that the margin of safety between the doses at which renal toxicity develops in animals and expected drug exposure in humans after the highest recommended dose is good according to the data in dogs, but poor according to the data in rats. However, it should be noted that the pharmacokinetic data submitted for this application were not sufficient for drawing firm conclusions (for reasons stated under "pharmacokinetics").

The renal toxic effects of teicoplanin were compared with those of vancomycin. An 8 day SC study was conducted in rats using teicoplanin, at doses of 25, 50 and 100 mg/kg/day and vancomycin at doses of 100 and 500 mg/kg/day. Both drugs caused a 10% decrease in plasma total protein levels, but neither drug had an effect on creatinine clearance or renal weight. Variable effects (mainly increases) were seen on urinary indicators of alkaline phosphatase, lactic dehydrogenase and leucine aminopeptidase activity. At necropsy, renal toxicity occurred with teicoplanin at doses of 50 and 100 mg/kg/day and with both doses of vancomycin (100 and 500 mg/kg/day). Both antibiotics produced similar lesions, which consisted of degeneration of the cortical tubular epithelia, associated fibrohistiocytic interstitial reactions, rare hyaline casts, slight dilatation of the cortical tubule lumen, and sporadic hypertrophy of the epithelia. This study suggests that the toxicity profile of teicoplanin is similar to that of vancomycin (as is the activity profile). The number of rats with affected kidneys at 100 mg/kg of teicoplanin was about the same or slightly less than that at 100 mg/kg vancomycin, suggesting that (on a dose for dose basis) the antibiotics are probably equally toxic to the kidneys. Vancomycin is used at doses of 500 mg every 6 h or 1 g every 12 h in humans. Therefore, assuming similar pharmacokinetics (including similar bioavailability) after SC administration in the rat, the potential for development of renal toxicity after administration of teicoplanin at 400 mg/day is about 5 times less than the risk associated with vancomycin at 2 g/day. However, since there is no information on the pharmacokinetics of vancomycin in animals, this study should be interpreted with caution.

In the pancreas, cytoplasmic vacuolization of acinar epithelia was found in rats at doses of ≥ 10 mg/kg/day in the 1 month SC studies, 20 mg/kg/day in the IV study, and at all doses in the 6 months study.

The only reported changes to the adrenals was hypertrophy at 150 mg/kg in one of the 1 month SC studies in rats, and vacuolization of cortical epithelia at 30 mg/kg in the 6 month study in rats.

In the liver, hepatocellular hypertrophy was seen at 20 and 40 mg/kg in the 6 month study in dogs. No abnormal histopathology was found in the spleen in either rats or dogs, but isolated changes to haemopoeitic processes were occasionally reported.

Increases in the weight of the gonads/uterus, and inflammation of the endometrium were found in the 6 month study in rats (at 3 and 6 month sacrifice), but not in the shorter studies in rats or in dogs. These effects, as with many of the other histological changes at the lower doses in rats, were reported to be reversible after withdrawal of the drug.

One month repeat dose toxicity studies were also carried out after oral administration in rats (200, 400, 800 and 1200 mg/kg) and dogs (100, 200, 400 and 800 mg/kg). No toxic effects were reported in dogs, and toxicity probably associated with drug retention in the gut (increased water intake, caecum and colon repletion) were seen in rats. The lack of systemic toxicity after oral administration of high doses is consistent with extremely poor oral absorption of teicoplanin.

Ophthalmology and auditory function

Ophthalmic examinations were conducted in the repeat dose toxicity studies in rats and dogs and found to be unremarkable. Ototoxicity was studied in the guinea pig using teicoplanin at doses of 25 mg/kg/day for 28 days. This dose gave exposure (as far as could be calculated) at least 17 times greater than that expected in humans. No evidence for ototoxicity was found in the preyer pinna reflex test, in electrophysiological examinations, or in counts of cochlear hair cells. After a single dose of 400 mg/kg teicoplanin, however, cochlear hair cell loss was 10% (compared with about 3% at lower doses of teicoplanin or in vehicle controls). The significance of this was not clear. Although evidence for ototoxicity was not found in the preclinical studies in guinea-pigs, there have been some suggestions that teicoplanin interferes with hearing in humans.

Mutagenicity and carcinogenicity

Teicoplanin, with and without S9 mix, did not show evidence of genotoxic activity at concentrations of 1-100 μg/plate in the Salmonella typhimurium test, 500-4000 μg/mL in the Saccharomyces cerevisiae D4 gene conversion test, and 250-200 μg/mL in the Schizosacharomyces pombe point mutation test.

In a study investigating male rat fertility, no evidence for a dominant lethal effect was found with doses up to 40 mg/kg/day. No clastogenicity studies were submitted.

No carcinogenicity data were submitted. Since teicoplanin is intended for relatively short term treatment, this is acceptable.

Reproductive toxicity

Reproductive toxicity studies with teicoplanin were conducted in rats and rabbits. A dose-range finding teratology study was carried out in rats and rabbits at SC doses up to 150 mg/kg. Teicoplanin up to 150 mg/kg from days 6-15 of pregnancy was found to be well tolerated in rats, but ≥ 25 mg/kg/day in rabbits from days 6-18 of pregnancy was associated with a high mortality rate and abortions in almost all surviving dams.

In the rat studies, teicoplanin at doses of 50, 100 and 200 mg/kg SC from days 6-15 of pregnancy was not associated with changes to pregnancy parameters or fetal parameters (including incidences of anomalies and abnormalities) in dams killed at 21 days of gestation. However, for dams allowed to litter, there was a significant reduction in the number of pups delivered alive (gestation survival index) at 100 mg/kg (90% survival) and 200 mg/kg (80% survival). The number of pups surviving over days 0-4 after delivery (0-4 day pup viability index) was also reduced at 200 mg/kg (86%), but there were no effects on survival over days 5-21 after delivery. A slight (5%) reduction in the gestation survival index was also seen at 40 mg/kg in the newly submitted rat study (see below). Therefore, it is possible that teicoplanin may be associated with increasing the likelihood of stillborn offspring even though the drug was not associated with an increase in the incidence of fetal death. There is no information about possible mechanisms involved in this effect. In the newly submitted study, it was reported that teicoplanin was not associated with difficulties during parturition.

The newly submitted rat reproductive toxicity study covered all aspects of male and female reproduction and offspring development using teicoplanin administered SC at doses of 10, 20 and 40 mg/kg. Although these doses were very low compared with doses able to be tolerated by (female) rats from the dose range finding study (see above), the duration of treatment was generally longer.

Toxic effects to males treated with teicoplanin prior to and during breeding for a total of 10 weeks included skin lesions at the site of treatment, reduced body weight at the HD, and adverse effects on the spleen. There were no apparent adverse effects on pregnancy parameters in untreated females mated with treated males or on fetuses at 21 days of gestation, and no evidence for a dominant lethal mutagenic effect.

Teicoplanin, administered SC to female rats at doses of 10, 20 and 40 mg/kg from 15 days prior to mating to up to 21 days postpartum, had no effects on female fertility and pregnancy parameters or fetal data at 21 days of gestation. There was also no evidence for teratogenic activity. However, at the 40 mg/kg dose, 5% of the pups were still-born (not statistically significant), and the total number of pups delivered (124) was slightly reduced compared with controls (151). In addition, the total litter weight from dams in all treatment groups was reduced 3-10% (not dose related). Similar findings were obtained in a peri- and post-natal development study in rats treated with the same doses from days 15 of gestation to day 21 post-partum. In this study, the total number of pups delivered at the HD (151) was reduced compared with controls (191), but there were no effects on pup survival. The total litter weight from dams in all treatment groups was consistently reduced by up to 10%, and this persisted for at least 21 days.

Treatment with teicoplanin was not associated with adverse effects on the behavioural, neurological, motor and reproductive development of (untreated) F_1 offspring, and did not affect F_2 pup development in rats.

Teicoplanin, at doses of 2.5, 5, 10 and 15 mg/kg/day administered SC from days 6-18 of gestation in rabbits, had no adverse effects on pregnancy or fetal parameters, and was not associated with an increased incidence of fetal abnormalities or malformations. Higher doses (≥ 25 mg/kg/day; used in the dose range finding) were associated with extreme maternal toxicity and abortions, making it difficult to determine whether there are direct effects on fetuses at doses higher than 15 mg/kg.

From the reproductive toxicity studies, it can be concluded that teicoplanin does not have teratogenic activity in rats at doses up to 200 mg/kg, and no teratogenic or embryotoxic activity in rabbits at doses up to 15 mg/kg. There was some evidence of embryotoxicity in rats since litter weight was consistently reduced by 10% at 10, 20 and 40 mg/kg/day in two separate studies. The significance of the increased incidence of stillborn offspring in rats treated with ≥ 40 mg/kg/day is uncertain, but a statement outlining these findings should be included in the Product Information.

Product Information

Pharmacokinetics

Detection and quantification of teicoplanin and any metabolites were not possible by the assay methods used in any of the studies in animals or (apparently) humans. Therefore, the following proposed statement should be omitted unless the clinical evaluator considers that there are adequate data to substantiate it:

> No metabolites have been identified; more than 97% of the administered teicoplanin is excreted unchanged.

Indications

Because of the relatively high risk of development of renal toxicity associated with clinical use of teicoplanin, it should be made clear that the drug is intended for use only if other treatments are not appropriate. Therefore, the indications should be:

> Targocid is indicated in the treatment of potentially life-threatening infections due to susceptible Gram-positive organisms in patients with organisms resistant to standard therapy (including methicillin and cephalosporins) or who are allergic to penicillins and cephalosporins. Such infections include endocarditis, septicaemia and osteomyelitis, respiratory infections, skin and soft tissue infections, urinary tract infections and peritonitis associated with chronic ambulatory peritoneal dialysis (CAPD).

The following paragraph should be amended to make it clear that teicoplanin should be used for prophylaxis only when other therapies are not suitable, and only if the potential benefits outweigh the risks: A suggested amendment is:

> Targocid is also recommended for prophylaxis in those patients who are resistant to standard therapy (including methicillin and cephalosporins) or who are allergic to penicillins and cephalosporins, but in whom infection with Gram-positive organisms would constitute a hazard (for example in patients requiring cardiac, dental or orthopaedic surgery).
>
> Targocid should be used for prophylaxis only if the benefits clearly outweigh the risks.

Carcinogenesis and Mutagenesis

The following statement should be included:

> Long-term studies in animals to evaluate the carcinogenic potential of teicoplanin have not been performed. Teicoplanin was negative in assays evaluating the potential to cause gene mutations, but assays to evaluate the potential to cause chromosome damage have not been performed.

Use in pregnancy and lactation:

It is recommended that the proposed statement:

> Although animal reproduction studies have not shown impairment of fertility, teratogenic, embryonic or fetotoxic effects, Targocid should not be used during confirmed or presumed pregnancy or during lactation unless the benefits outweigh possible risks.

should be substituted with the following:

> Reproductive studies in rats and rabbits with SC doses up to 200 mg/kg/day and 15 mg/kg/day respectively did not reveal teratogenic effects. Targocid was associated with an increase in the number of stillborn pups when rats were treated SC with doses ≥ 100 mg/kg/day. Pup weight was reduced at all doses tested (SC doses of ≥ 10 mg/kg/day). It is not known if Targocid is excreted in breast milk during lactation.
>
> Targocid should not be used during confirmed or presumed pregnancy or during lactation unless the benefits outweigh possible risks.

A suggested category for use in pregnancy is B3.

Dosage and administration

Children:

No preclinical studies were conducted in young animals. Because of the lack of preclinical information on potential toxic effects in the young, it is suggested that the maximum recommended dose for children should not exceed that proposed for adults, and the PI should be amended accordingly. The sentence stating dosage in children should be replaced with the following:

> In patients under 14 years, doses of 6 mg/kg should be given at intervals of 12 h on the first day, followed by 3 mg/kg daily.

The following sentence in the PI should be omitted unless the clinical evaluator considers it is justified:

.....Doses of up to 12 mg/kg daily are recommended in granulocytopenic patients.

Unless there is adequate clinical experience with teicoplanin in children, it should be made clear that the risks associated with the use of teicoplanin in children are not known.

Recommendations

By todays standards, the preclinical data submitted in support of the application to register teicoplanin were not sufficient. The pharmacokinetic data in particular were poor, and there were limited secondary pharmacology studies. In addition, no studies on the potential clastogenic properties of teicoplanin were conducted despite requests by the TGA for this information.

The kidney was identified as the primary target organ for the toxic effects of teicoplanin. Drug-related changes were also observed at the injection site and in a number of other organs. Trough plasma levels at which renal toxicity was observed in animals compared with trough levels expected in humans after the highest recommended dose were about 8-14 times greater in dogs after 1 month of treatment (lower margins after 6 months treatment), but < 1 to 2.4 times greater in rats after 1 or 6 months of treatment. Thus, the safety margin for the development of renal toxicity was good according to the data in dogs, but poor according to the data in rats. However, it should be noted that because of the poor pharmacokinetic data (including lack of metabolic studies), the suitability of either species as a model for humans is uncertain. The renal toxic effects in all of the dog studies and in the 6 month rat study were reversible over 9-10 weeks after treatment had ceased.

The nephrotoxicity of teicoplanin, on a dose for dose basis, was found to be comparable to that of vancomycin in an 8 day SC study in rats. However, this study was of limited use because of the absence of pharmacokinetic data for vancomycin.

In conclusion, there were considerable deficiencies in the preclinical data. The kidneys were identified as the target organs for toxicity, and there was evidence to suggest that the effect may be clinically relevant. However, teicoplanin has similar properties to vancomycin, and may, in some cases, be of some clinical advantage. Therefore, from a preclinical point of view, there are no objections to the registration of teicoplanin provided that its use is restricted to cases where vancomycin would normally be used. Preclinical approval is also based on assumptions that the clinical evaluator has assessed the issues associated with possible adverse renal effects, and that this is reflected in the product information.

[redacted]

Drug Toxicology
Evaluation Section

23-Sep-1993

[redacted] 23-9-93

Preclinical Evaluation of Teicoplanin

1 INTRODUCTION

Teicoplanin is a glycopeptide antibiotic obtained as a fermentation product of Actinoplanes teichomyceticus, and chemically related to the vancomycin-ristocetin group of antibiotics. It is active against aerobic and anaerobic gram-positive bacteria, including methicillin-resistant staphylococci, Group D streptococci, Clostridium difficile and group JK corynebacteria. It has bactericidal activity against susceptible bacteria, and resembles vancomycin in the manner in which it interferes with bacterial cell wall synthesis.

A detailed preclinical evaluation of teicoplanin has been prepared previously for a clinical trial application. This was approved on 7 May 1987 (ref 86/9011). The current application is to register teicoplanin powder (to be made up as a solution for IM or IV administration) for use in a wide range of bacterial infections (see proposed clinical use). A comprehensive reproductive toxicity study only was submitted for the current application, and evaluation of this has been incorporated into the previous evaluation for the clinical trials.

1.1 Proposed clinical use

Teicoplanin is indicated for the treatment of aerobic and/or anaerobic gram-positive bacterial infections such as endocarditis, septicaemia and osteomyelitis, infections of the skin, soft tissues and urinary tract, and peritonitis associated with chronic ambulatory peritoneal dialysis. It is intended for use in patients who are allergic to penicillins and/or cephalosporins, or who are resistant to standard therapy, including resistance to methicillin. Teicoplanin is also intended to be used prophylactically against potential infection with gram-positive organisms in surgical patients.

1.2 Dosage and administration

Teicoplanin is to be administered IV or IM at a dose of 400 mg (about 6 mg/kg) on the first day, and at 200 or 400 mg on subsequent days. The higher dose and the IV route are recommended in severe infections. Two doses of 400 mg on the first day and once daily thereafter are recommended in life threatening conditions. Duration of treatment has not been specified, but it is suggested that this would depend on the condition being treated and on the clinical response. For example, in a letter to the TGA, it was pointed out that therapeutic responses have been shown to occur within 48-72 h in most patients, whilst treatment for 3 weeks or longer is recommended for conditions such as endocarditis and osteomyelitis.

1.3 Chemical and formulation details

<u>Other names and company code number</u>: DL 507 IT; Teichoplanin was previously known as teichomycin. Prior to 1984 the company used the name teichomycin in all reports, but in 1984 the name was changed to teicoplanin which has been used in all subsequent reports.

Relationship to other drugs: Teicoplanin is chemically related to the vancomycin-ristocetin group of antibiotics.

Chirality and impurity profile: Teicoplanin is a mixture of six components which contain the sugars α-D-mannose and N-acetyl-B-D-glucosamine, and are differentiated only by the substituent R1, which may be H or another sugar. Teicoplanin can be subdivided into two major components; teicoplanin A3 (6-14%), and teicoplanin A2 (86-94%) which has 5 sub-fractions that can be identified using the criteria described above. The percentage composition of teicoplanin used in the preclinical and clinical studies falls within the limits (percentage) of amounts of teichomycin A2 and A3 described above. A detailed breakdown of the composition of teicoplanin used in the preclinical studies and clinical studies is shown table 1 (appended).

In all studies described in this report, formulations of teicoplanin included all relevant fractions of teicoplanin (A2 and A3).

Formulation: Teicoplanin is to be marketed as vials containing 100 200 and 400 mg quantities of lyophilised teicoplanin powder plus 10 mg (for 100 mg strength) or 20 mg (for 200 and 400 mg strength) of NaCl. An ampoule of water for reconstituting the solution is included.

1.4 Overseas status

As of 1991, teicoplanin was approved for use Italy, UK, Denmark and Holland. Evaluations in Sweden, Canada and USA had not been completed.

2 PHARMACOLOGY

2.1 Mechanism of action

Teicoplanin has both bactericidal and bacteriostatic (inhibition of cell wall biosynthesis) activity. At concentrations 5 to 10 times its MIC, teicoplanin killed 99.9% of Staphylococcus epidermidis by 5 hours, and 99.9% of Staphylococcus aureus and Streptococcus pyogenes. The bacteriostatic mode of action of teicoplanin is similar to that of vancomycin which selectively inhibits cell-wall biosynthesis by inhibiting peptidogylcan polymerisation.

2.2 *In vitro* activity against gram-positive bacteria

Teicoplanin was compared with several antibiotics used for gram-positive infections. In this study teicoplanin was dissolved in dimethylformamide and diluted in 0.067 M phosphate buffer, pH 7.38. All other antibiotics were dissolved and diluted in phosphate buffer. Minimum inhibitory concentrations (MICs) were determined by the two-fold dilution method. Strephylococci were tested in Difco brain heart infusion plus 2% bovine serum and staphylococci in Difco "Antibiotic Medium No 3".

Teicoplanin was active against all gram-positive aerobes tested (table 2; appended). Teicoplanin had high activity against Streptococcus pyogenes and Streptococcus pneumoniae (MIC_{90} = 0.1 µg/mL), Streptococcus faecalis and Staphylococcus aureus (MIC_{90} = 0.4 µg/mL), and other streptococci (MIC_{90} = 0.2 µg/mL). The effects of changing parameters like inoculum size, serum concentration and pH of medium on the MIC values of teicoplanin were negligible (no data presented).

The in vitro activity of teicoplanin against gram-positive anaerobic bacilli was studied in bacteria cultures grown on Wilkins-Chalgren agar. The results displayed in table 3 (appended) show teicoplanin to be marginally more potent than vancomycin against Clostridium perfingens, C. difficile and C. septicum, Propionibacterium acnes and Listeria monocytogenes, while both antibiotics have similar activities against gram-positive aerobic diptheriods.

Teicoplanin was active against multiresistant clinical strains of Staphylococcus aureus (5 isolates), Streptococcus pnuemoniae (7 strains), Staphylococcus epidermidis (7 strains), and Streptococcus faecalis (1 strain) (table 4, appended; MIC values ranged from 0.1 to 1.6 µg/mL). All of these strains were sensitive to both teicoplanin and vancomycin.

2.3 In vitro activity against other micro-organisms

Teicoplanin was not active (MIC 100 mg/mL) against Pseudomonas aeruginosa, Candida albicans, Trichophyton mentagrophytes, Mycobacterium tuberculosis and Mycoplasma gallisepticum. MIC values of between 10 to 20 µg/mL were recorded for teicoplanin against Proteus vulgaris and Escherichia coli.

2.4 In vivo antimicrobial activity

Mice

Groups of 10 mice (5/sex) were infected IP with 0.5 mL of a bacterial suspension prepared by diluting overnight cultures either in peptonized saline (Streptococci pyogenes and pneumoniae) or in 10% Difco bacteriological mucin (Staphylococcus aureus). Animals were treated with teicoplanin SC once daily for three days starting after infection. The ED_{50} in mg/kg/day was calculated on the 10th day.

The MIC values for a series of antibiotics in vitro are shown in table 2 and it is apparent that teicoplanin was the most effective agent against Staphylococcus aureus and Streptococcus pneumoniae as well as being very potent against Streptococcus pyogenes. This was also the case in vivo.

Rabbits

The effect of treatment with teicoplanin on methicillin-resistant Staphylococcus aureus was studied in NZ rabbits. Endocarditis of the aortic valve in rabbits was established by the method of Perlman and Freedman using both methicillin-resistant (MR) and methicillin-sensitive (MS) Staphylococcus aureus. Comparisons between teicoplanin, vancomycin and nafcillin were carried out, with teicoplanin and vancomycin being tested against MR infections, and teicoplanin and nafcillin used against MS infections. Teicoplanin was as effective as the reference antibiotic in both MS and MR infected rabbits.

The treatment of experimental endocarditis due to Staphylococcus epidermidis with IV teicoplanin and rifampicin was studied in rabbits. Both antibiotics were equally effective at combating the bacteria from blood cultures, while rifampicin was more effective (50%) at clearing bacteria from the blood stream. Survival of the animals in the study was improved by teicoplanin (9/14) and rifampicin (9/11) when compared with controls (3/11).

A further study of experimental endocarditis (Streptococcus faecalis) in rabbits was used to evaluate teicoplanin, gentamicin and ampicillin, alone and in paired combinations. Dosages given (by indwelling transvalvular catheter) produced peak serum levels similar to those considered therapeutic in humans (teicoplanin 36.2 μg/mL, ampicillin 61.7 μg/mL, gentamicin 8.4 μg/mL). Teicoplanin was found to be as effective as the other antibiotics with regard to reducing bacterial vegetations. The combination of teicoplanin and gentamicin (only one dose-combination used) was more effective (2.5 times) than teicoplanin alone at reducing bacterial vegetation.

2.5 Interactions *in vitro*

The interaction of both teicoplanin and vancomycin with the bactericidal activity of normal human polymorphonucleocytes (PMN) and monocytes, which are defective in the intracellular killing of Staphylococcus aureus, was investigated in cells isolated from a patient affected by chronic granulomatous disease (CGD). Teicoplanin, but not vancomycin, enhanced the intracellular killing by PMN and monocytes when the cells were pretreated with 10 μg/mL of teicoplanin for 1 hour at 37°C.

In vitro interactions of teicoplanin and/or vancomycin with rifampicin (aminoglycosides) were described in 2 articles. When tested in combination with rifampicin, both teicoplanin and vancomycin exhibited neither antagonism nor synergism against staphylococci, streptococci and several gram-positive anaerobes. However, in a second published study, teicoplanin and either rifampicin, streptomycin, gentamicin or tobramycin combinations were more effective (greater synergism) than combinations of these aminoglycosides with vancomycin.

3 SECONDARY PHARMACOLOGY

3.1 Effects on the cardiovascular system

The cardiovascular effects of teicoplanin administered IV were assessed in both the anaesthetised and conscious dog. In the conscious dog, teicoplanin, at a dose of 10 mg/kg, had no effect on mean arterial blood pressure, heart rate, cardiac contractility, electrocardiographic examination and gross behaviour. In the anaesthetised dog, the same dose of 10 mg/kg produced a small but significant decrease in mean arterial blood pressure (7% at 2 hours post-dosing), cardiac output (25%) and stroke volume (26%). The decrease in cardiac output resulting from the administration of teicoplanin in the anaesthetised dog was probably due to a decrease in venous return rather than a decrease in the contractile state of the myocardium since dP/dt was not significantly altered. The difference in responsiveness of conscious compared to anaesthetised dogs was probably due to a dampening of homeostatic mechanisms during anaesthesia.

Teicoplanin given to normotensive rats at a dose of 60 mg/kg/day (IP or SC) for five consecutive days did not modify the systolic blood pressure and heart rate of the animals (no data presented).

3.2 Effects on the CNS

Statements were made that behaviour in the rat was not affected by 3 mg/kg (IP) of teicoplanin, but higher doses of up to 60 mg/kg (IP) slightly and specifically modified the normal behaviour. Furthermore, at 300 mg/kg (IP) important CNS depressant effects were observed. These statements were not supported since no data were presented, and it is unclear what the nature of the behavioural changes were. It was further stated that similar findings were reported in mice up to the maximum dose tested (600 mg/kg).

It was also stated that teicoplanin given to mice at 30 mg/kg (IP) did not prevent convulsions induced by electroshock, or convulsions and death induced by pentetrazol or strychnine (no data presented).

3.3 Effects on platelets

Teicoplanin, over a concentration range of 10-5000 μg/mL _in vitro_, did not cause platelet aggregation or release of serotonin from human platelet-rich plasma. Vancomycin, at 5000 μg/mL, induced 5-HT release but not aggregation. Ristocetin, an antibiotic similar in structure to teicoplanin, induced platelet aggregation and 5-HT release (dose-related) at concentrations above 600 μg/mL.

4 PHARMACOKINETICS

For the following studies, teicoplanin was dissolved in dimethylformamide and diluted in phosphate buffer unless stated. Concentrations of unlabelled teicoplanin and active metabolites were determined microbiologically with _Bacillus subtilis_ L107 (a derivative of strain ATCC 6633). The sensitivity of this method was ≤ 0.7 mg eq/L. Teicoplanin labelled with [^{14}C] was biosynthesized through fermentation of [^{14}C]-glucose by _Actinoplanes teichomyceticus_. The specific activity was 0.95-1.17 μCi/mg. Total radioactivity in samples was determined by LSC after appropriate treatment. However, the sponsor suggests results of this assay should be interpreted cautiously, partly because the nature of the radiolabelled compound/s formed by the biosynthetic technique was not defined. In some experiments, levels of radiolabelled compounds were also determined by microbiological assay.

4.1 Rats

4.1.1 Absorption

Oral absorption

Absorption of teicoplanin was investigated in situ in anaesthetised male Wistar rats in which segments of jejunum were isolated. Blood was collected directly from the vascular supply of the isolated loop and analysed for plasma bioactivity. The rate of appearance of teicoplanin and/or related compounds in plasma was 0.6 μg eq/min/g intestine. In a separate set of rats, urinary excretion of bioactivity over 24 h accounted for < 0.6% of a 100 mg/kg oral dose of teicoplanin, which also suggests very poor oral absorption of teicoplanin since the drug is excreted predominately in the urine in rats (section 4.3)

Absorption of teicoplanin was investigated in female Fischer rats given a single oral dose of [^{14}C]-teicoplanin (8.3 mg/kg) after 7 days of oral dosing with 20 mg/kg unlabelled teicoplanin. Rats (5/time point) were killed at 10, 24, 48, 96, 168 and 336 h after [^{14}C]-teicoplanin was administered.

Whole blood levels of radioactivity were very low at 0.036 ppm 10 h after dosing, and declined to ≤ 0.013 ppm at 4 days. Investigations of tissue distribution and excretion (sections 4.1.2 and 4.1.3) in these rats were also consistent with very poor oral absorption of teicoplanin.

Plasma kinetics

Male Wistar rats received teicoplanin at IV doses of 20 mg/kg, and blood samples were taken at 0.5, 1, 2, 4, 8 and 24 h. The plasma concentration of teicoplanin and/or active metabolites was 75 μg eq/mL at 30 min, and 2.8 μg eq/mL at 24 h. The elimination of bioactivity from plasma was biphasic, with t½(0.5-2 h) of 2 h and t½(8-24 h) of 6 h being calculated.

In another study, Sprague-Dawley rats received a single dose of [^{14}C]-teicoplanin (20 mg/kg; in saline) IV (4/sex/group) or IM (4 males). Findings are summarised in the table:

	Intravenous					Intramuscular		
	C0 μg eq/mL	t½ h	AUC μg eq.h/mL	VD L/kg	Cl mL/h	Cmax* μg eq/mL	t½ h	AUC μg eq.h/mL
Males	256	22.4	758	0.85	23.8	8.8	32.1	442
Females	343	22.4	950	0.69	21.2	Not determined		

*Cmax was observed at 8 h after IM administration. AUC was determined over 0-72 h (IV) or 0-96 h (IM).

It should be noted that plasma levels in males were 25-30% lower than plasma levels in females throughout the period of sample collection. The sponsor attributed this to the smaller volume of distribution in females. A similar difference between male and female plasma levels was also evident in the 1 month SC toxicity studies (see table below).

Plasma levels of radioactivity after IM administration increased slowly from 2.7 μg eq//mL at 15 min to a peak of 8.8 μg/mL at 8 h, and then declined slowly to 1.1 μg eq/mL at 96 h. Plasma levels of radioactivity after IM administration were markedly lower than levels after IV administration for about 20 h (the IM AUC is only about 42% of the IV AUC over 0-72 or 96 h), but IM levels remained about 30-40% higher than IV levels over 24-72 h. Furthermore, plasma radioactivity was detected at 96 h after IM, but not IV administration, suggesting slower drug clearance after IM administration.

Compared with peak plasma levels, 24 h plasma levels were about 98% lower after IV dosing, but only about 18% lower after IM dosing.

Plasma levels of drug-related compounds were also determined by microbiological assay. Compared with measurements of total radioactivity from 0.05-8 h after drug administration, the microbiological assay accounted for ≤ 30% of the compounds in plasma after IV administration (males and females), and about 30-50% of the drug related compounds in the plasma after IM administration. This suggests that a large proportion of the drug-related compounds in plasma are inactive metabolites.

The sponsor suggests that caution should be used in interpreting these results, and any meaning attributed to these findings should not be emphasised since measurements of drug-related compounds excreted in the urine were similar after assessment by either LSC or microbiological assay, suggesting that most of the excreted compounds were biologically active. This is inconsistent with the above findings for plasma compounds, but the reasons for this are not clear.

Plasma levels from toxicity studies

The plasma levels of teicoplanin and/or active metabolites were determined by microbiological assay during the repeat dose toxicity studies. Plasma concentrations (μg eq/mL) 24 h after the dose indicated are summarised below:

One Month IV Study
No. of doses

Dose mg/kg/day	**31**	**32**
10	1.4	0.96
20	3.2	1.81
40	4.9	4.3
80	13.4	9.5

N = 10/sex/group. See section 6.1.1.

One Month SC Study
31st dose

Dose mg/kg/day	Males	Females
25	10.4	6.9
50	21.7	16.9
100	36.7	46.4
150	83.8	45.6

N = 10/sex/group. See section 6.1.2.

Six Month SC Study
No. of doses

Dose mg/kg/day	7	92	183
5	< 0.58	1.9	2.5
10	< 0.58	6.1	6.1
30	2.6	9.1	13.8

N = 26/sex/group. See section 6.1.4.

One Month PO Study
No. of doses

Dose mg/kg/day	1	8	29
200	0	0	0
400	trace	0	0
800	trace	0	0
1200	1.54	0.76	0

Assay limit of detection was 0.7 μg/mL
N = 10/sex/group. See section 6.1.5.

4.1.2 Distribution

The tissue distribution of teicoplanin was investigated in male Sprague-Dawley rats (4/time point) which received 10 mg/kg of [^{14}C]-teicoplanin by IM injection. Tissue levels were recorded as μg eq/g of fresh tissue, and the ratio of teicoplanin in the tissue to its concentration in the plasma (tissue/plasma; T:P ratio) was measured. Tissue sampling was carried out at 6, 24 and 48 hours after drug administration. The T:P ratio in descending order is shown in the table:

T:P ratio at various times

Time	6 h	24 h	48 h
	Kidneys (1.66)	Kidneys (7.41)	Kidneys (23.86)
	Adrenals (1.54)	Adrenals (6.49)	Adrenals (20.35)
	Intestine (1.54)	Liver (4.13)	Liver (14.94)
	Stomach (1.24)	Intestine (4.06)	Femur (13.56)
	Lungs (1.13)	Spleen (2.52)	Spleen (5.35)
	Others (< 1)	Femur (2.08)	Intestine (4.09)
		Lungs (1.44)	Lungs (2.47)
		Stomach (1.01)	Stomach (1.58)
			Fat (1.19)
			Heart (1.07)

Following IM administration of 10 or 20 mg/kg [^{14}C]-teicoplanin, drug diffusion away from the injection site appeared to be slow, with the percentage dose retained in the leg being 73% at 6 h, 21% at 24 h and about 10% at 48 h and at 96 h.

Tissue distribution of teicoplanin and related compounds was also investigated in female Fischer rats (5/time point) administered a single oral dose of [^{14}C]-teicoplanin (8.3 mg/kg) following 7 days of oral dosing with 20 mg/kg unlabelled teicoplanin.

Consistent with very poor oral absorption of teicoplanin, absolute levels of radioactivity in fat, liver, kidney, muscle and the GIT were very low, ranging from about 0.3-0.9 μg/g tissue at 10 h to ≤ 0.002 μg/g after 7 days. However, relative to whole blood levels, high levels of radioactivity were detected in the following tissues (T:P ratio from 10 h-7 days in brackets): fat (26-6), liver (12-2) and kidney (7-4). Smaller amounts of radioactivity were found in the muscle (T:P ratio of 2-≤ 1) and GIT (T:P ratio of 6-2).

4.1.3 Excretion

Urinary excretion of bioactivity was determined in male Wistar rats following a single IV (20 mg/kg) or oral (100 mg/kg) dose of teicoplanin. The findings are summarised in the table.

Cumulative urinary excretion in rats
% of the administered dose

Time (h)	IV	PO
0-8	31.4	< 0.03
0-24	51.8	< 0.06
0-48	54.5	-

At most, about 1% of the dose was recovered in the bile over 4 h after IV administration. These results suggest that teicoplanin is excreted predominantly in the urine after IV administration.

Low levels of bioactivity after oral administration are consistent with very poor oral absorption of teicoplanin (section 4.1.1). This was confirmed in a study in female Fischer rats (5/time point) administered a single oral dose of [^{14}C]-teicoplanin (8.3

mg/kg) following 7 days of oral dosing with 20 mg/kg unlabelled teicoplanin. Rats (5/time point) were killed at 10, 24, 48, 96 and 168 h after drug administration, and a further 5 rats were killed 14 days after treatment.

A total of 98.4% of the dose was recovered within 7 days of drug administration, with most of this (87%) excreted rapidly within the first 24 h, and then more slowly over subsequent days. Most of the radioactivity (83% of the dose) was recovered in the faeces in the first 24 h after dosing, with much smaller amounts detected in the urine (2.8%) and in expired air (1.4%) at this time.

Excretion of teicoplanin and/or metabolites was also determined in 4 male Sprague-Dawley rats which received 20 mg/kg of [^{14}C]-teicoplanin by IM injection. The concentration of teicoplanin and/or metabolites in urine was determined by both LSC and by microbiological assay. Total radioactivity only was measured in faeces.

At 4 days after drug administration, a total of 47% of the dose was recovered in urine and 15% was recovered in faeces. A plot of the excretion results indicated that neither urinary excretion or faecal excretion of compounds had reached a plateau. The greatest proportion of the dose recovered in urine was found in the 8-24 h fraction (21% of the dose), with smaller amounts recovered in other fractions (10% at 24-48 h and 4% at 48-72 h). About 3-5% of the dose was excreted in the faeces each day.

Measurement of drug-related compounds excreted in each fraction of urine using either radiochemical analysis (LSC) or microbiological assay produced almost identical results, suggesting that urinary excreted compounds are probably teicoplanin and/or biologically active metabolites. This finding was inconsistent with findings that a large proportion of the plasma compounds were probably inactive metabolites (section 4.1.1), but the physiological significance of the discrepancy is questionable.

4.2 Mice

4.2.1 Absorption

Teicoplanin, at doses of 1, 5 and 10 mg/kg, was administered SC to 5/sex/group CF1 mice. Peak plasma levels of teicoplanin and related compounds were attained at 0.5 h regardless of dose given. Findings are given in the table:

Dose (mg/kg)	Cmax (µg eq/mL)	T½ (h)	AUC(0-8 h) µg eq.h/mL
1	2	2.5	7.0
5	16	2.5	57.8
10	31	2.2	106.4

It should be noted that the increase in Cmax and AUC was greater than dose proportional from 1 to 5 mg/kg, but linear from 5 to 10 mg/kg. The elimination half life of radioactivity was not altered by dose.

4.3 Dogs

4.3.1 Absorption

Plasma kinetics

The pharmacokinetics of teicoplanin dissolved in saline or povidone (old formulation which was used in some toxicity studies) were determined in male Beagle dogs. The first group of 3 dogs received 5 mg/kg teicoplanin in saline IV and, after a 10 day washout period, another IV dose at 40 mg/kg. A second group of 3 dogs received 5 mg/kg teicoplanin in saline by IM injection and, after a 10 day washout period, 5 mg/kg of teicoplanin in 2.5% povidone by IM injection. Plasma levels of active drug-related compounds were determined by a microbiological assay. Findings are summarised in the table:

	Route	C0/Cmax μg eq/mL	$t_{½}$ h	VD L/kg	Cl mL/h/kg	AUC(0-∞) μg eq.h/mL	AUC L/h
5 mg/kg	IV	70	27	0.32	8.5	822	10.6
40 mg/kg	IV	565	28	0.32	8.0	6001	11.7
5 mg/kg	IM	21 (2 h)	30	0.35	8.1	742	11.9
5 mg/kg*	IM	19 (8 h)	28	0.30	7.4	640	12.9

* represents teicoplanin in the old formulation (in povidone).
AUC was determined over 0-96 h (5 mg/kg) or 0-120 h (40 mg/kg).

The findings indicate linear pharmacokinetics over the dose range of 5-40 mg/kg IV in the dog. The bioavailability of the 5 mg/kg IM administered dose of teicoplanin was 90%. It was concluded that, at 5 mg/kg IM, the pharmacokinetics of teicoplanin in povidone were similar to those with teicoplanin in saline, but absorption appeared to be slower.

Calculations of the minimum plasma level of teicoplanin and related compounds were based on the assumption that pharmacokinetic parameters remained constant with repeated administration at a given dose levels. It was estimated that the minimum plasma concentration of drug-related compounds at steady state would be about 19.5 μg eq/mL after IV or IM administration of 5 mg/kg (16.6 μg eq/mL with old formulation), and 131 μg eq/mL after 40 mg/kg IV. It was estimated that steady state would be reached after 5-6 doses given at 24 h intervals.

Plasma levels from toxicity studies

The plasma levels of teicoplanin and/or active metabolites were determined by microbiological assay during the repeat dose toxicity studies. Plasma concentrations (μg eq/mL) 24 h after the dose indicated are summarised below:

One Month IV Study
No. of doses

Dose mg/kg/day	1	7	28
5	8.2	16.6	19.2
10	18.0	32.9	33.5
20	33.6	52.8	64.4
40	69.3	128.9	137.7

N = 2/sex/group. See section 6.2.1.

One Month IM Study
No. of doses

Dose mg/kg/day	1	7	28
5	8.4	15.1	18.3
10	15.8	32.3	38.8
20	28.8	52.8	69.9
40	61.9	123.1	146.5

N = 2/sex/group. See section 6.2.2

Six Month IM Study
No. of doses

Dose mg/kg/day	7	91	182
10	38.6	37.7	38.9
20	65.2	64.4	62.9
40	147.2	129.2	119.0

N = 8/sex/group. See section 6.2.3

One Month PO Study
No. of doses

Dose mg/kg/day	1	7	28
100	trace	trace	trace
200	trace	trace	trace
400	trace	2.04	2.15
800	1.27	2.97	3.73

Assay limit of detection was 0.7 μg/mL
N = 2/sex/group. See section 6.2.4

4.3.2 Excretion

The urinary excretion of teicoplanin and/or related compounds was assessed in dogs used for the plasma kinetics studies (section 4.3.1). About 50% of either the 5 or 40 mg/kg IV dose was excreted cumulatively over 5 days. A significantly greater proportion of the dose (about 65%) was excreted cummulatively over 5 days after the 5 mg/kg IM dose, with no differences seen with the two teicoplanin formulations. In all cases, about 30-40% of the drug was found in urine in the first 24 h, after which time a plateau was reached.

In a preliminary study using one dog, plasma levels of teicoplanin and/or related compounds were similar when biliary processes were intact or interrupted, and no drug related compounds were detected in bile over 48 h after drug administration, suggesting that biliary excretion was not substantial in the dog.

4.4 Guinea-pigs

4.4.1 Absorption

Plasma Kinetics

Some pharmacokinetic data in guinea-pigs was determined during the ototoxicity study (section 6.3). Teicoplanin (in povidone) was administered SC to 4 female Dunkin-Hartley guinea-pigs at a dose of 25 mg/kg, 3 times at a day for 28 days. The concentration of teicoplanin and/or active compounds in plasma samples (from 2-3 animals/time point) was determined using a microbiological assay.

Maximum plasma drug levels were about 30 μg eq/mL over 4-8 h after the first dose of 25 mg/kg teicoplanin, and declined to about 5 μg eq/mL by 24 h. The drug half life was 5.8 h.

Plasma drug levels were 72 μg eq/mL at 4 h after the last dose of the study, and no drug (detection limit 7.2 μg eq/mL) was detected in the perilymph fluid after the first or last dose of teicoplanin. The sponsor suggests that drug accumulation after repeated dosing is to be expected given the long half life of the drug.

4.5 Humans

The following summary information is taken from the clinical evaluation of the registration application for teicoplanin. Levels of teicoplanin and related compounds were determined by a microbiological assay.

4.5.1 Absorption

After IM administration of teicoplanin to healthy volunteers, bioavailability compared with IV dosing was 94%, approximate Cmax after 3 mg/kg IM was 7.1 μg eq/mL at 2 h, and peak and trough levels were maintained during 5 repeated doses.

Maximal concentrations after IV dosing of 3 and 6 mg/kg were 54 and 112 μg eq/mL respectively. At 24 h after dosing, plasma levels had fallen to 2.1 μg eq/mL after 3 mg/kg and 4.2 μg/mL after 6 mg/kg; AUC(0-∞) was 256 and 521 μg eq.h/mL respectively. The elimination half life was 47 and 44 h; V_D was 59 and 55 L, and distribution was described as fitting a prolonged biphasic, 3 compartment model. Teicoplanin was not absorbed in humans after oral dosing.

Peak plasma levels of teicoplanin 2 h after an IM dose of 3 mg/kg was 7.1 μg eq/mL, and levels dropped to 2.3 μg eq/mL at 24 h after drug administration. AUC(0-∞) was 231 μg eq.h/mL, the elimination half life was 48 h; V_D was 69 L.

Pharmacokinetic parameters were also determined in renally impaired individuals (moderate and severe renal impairment) and in elderly patients. These were compared with parameters in healthy volunteers. The summary table is reproduced below:

Subjects	Cl* mL/min	Cl mL/h/kg	T½ h	AUC mg.h/L
Healthy	107	9.3	62	197
Moderate**	57	3.2	96	326
Severe **	12	0.6	111	409
Elderly	51	3.8	114	-

* Cl = creatinine clearance; ** = degree of renal impairment; Teicoplanin was administered at a dose of 3 mg/kg IV in each case.

Excretion of teicoplanin is greatly reduced in renally impaired individuals, but drug accumulation has reportedly not been associated with toxicity, and no special modifications to dosing regime is suggested. Pharmacokinetic parameters in elderly patients resemble those found in patients with moderate renal impairment. Elderly patients also have a greatly increased V_D, suggested to be due to a greater proportion of fat in this group. No alterations in the dosage regime are suggested for this patient population.

The half life of teicoplanin appears to vary considerably between studies, with values ranging from 30-70 h (mean of 51 h) being reported in 7 studies using healthy volunteers.

Pharmacokinetic information in children is limited, but it appears that drug half life is reduced in these patients.

4.5.2 Distribution

Teicoplanin is 90% bound to plasma proteins with little distribution to red blood cells and CSF. Physiologically relevant levels are found in bone, synovial fluid, lung tissue, pleural fluid, fat, blister fluid and peritoneal fluid.

4.5.3 Metabolism

Teicoplanin does not appear to undergo extensive metabolism after systemic administration. After a (parenteral) dose of 400 mg, 80% of the drug is excreted unchanged in urine up to 16 days after administration.

4.5.4 Excretion

As indicated under the metabolism section, the main route of excretion for teicoplanin after parenteral administration is in the urine. The elimination T½ is long (range, 70-100 h in patients; 62 h in volunteers); total body clearance was 15.7 mL/h/kg, and renal clearance was 9.3 mL/h/kg. These parameters are not altered by route of administration, repeated dosing or dose.

5 ACUTE TOXICITY and LOCAL TOLERANCE

Acute toxicity studies were performed at G. Lepetit Research Laboratories (Italy), and complied with GLP.

5.1 Acute toxicity of teicoplanin in the rat, mouse and dog.

The results of a number of LD_{50} studies are shown in the table:

LD_{50} (mg/kg)

Route	Mouse (CF1)	Rat (S-D) 7 day	Rat (S-D) 14 day	Dog (Beagle)
PO	> 15000	> 10000	-	-
IP	1050	540	540	-
SC	2860	3470	2500	
IM	-	-		> 900
IV	715	106	-	750

Clinical signs associated with the administration of teicoplanin were: sedation, ptosis, dyspnoea, loss of weight, piloerection and injection site ulceration. Surviving animals (mice and rats) were sacrificed and examined at 14 days after the last dose. There were signs of liver and kidney damage (tissue colour changes, renal calculi, and increases in the size of the organ) in rats treated IP with doses of 250, 500 and 750 mg/kg. No lesions were found in rats treated PO or IV, or in mice, but very few of the rats had survived the treatment and were therefore not autopsied.

Deaths occurred from doses of 600 mg/kg IV, 750 mg/kg IP and 2000 mg/kg SC in mice; and from 90 mg/kg (not 80 mg/kg) IV, 500 mg/kg (but not 250 mg/kg) IP and 2000 mg/kg SC in rats. In general, deaths after IV or IP administration occured within 24 h, whilst deaths after SC administration occurred over a number of days, especially during days 4-6 and 8-14. Dogs treated with 750 or 900 mg/kg IV died, but there were no other deaths with the other IV doses or after other routes of administration in dogs.

In the dogs, sedation, muscular tremors, ataxia, dyspnoea, anorexia, salivation, vomiting, body weight loss and swelling at the injection site were observed. At autopsy, the kidneys were enlarged and histopathological examination revealed necrosis of the epithelia of mainly cortical tubules. Renal (degenerative and necreotic changes) and gastrointestinal (haemorrhagic gastroenteritis) lesions were found in dogs treated with doses starting from 600 mg/kg IV or IM. There were no reports of lesions at 300 mg/kg.

5.2 Local Tolerance studies

Local tolerance studies were conducted at G. Lepetit Research Laboratories (Italy) using various vehicles and routes of administration. The vehicle formulation used in clinical trials and that proposed for registration is saline.

5.2.1 Dogs

IV study with teicoplanin in distilled water (May 1981).

Teicoplanin in distilled water was administered IV to one Beagle dog/sex/dose level at the concentration of 50 mg/mL. The solution was given at doses of 10, 40 and 80 mg/kg/day for 7 consecutive days, and saline controls were included. All animals were killed at the end of the 7 day treatment and local reactions were evaluated by gross and histological examinations.

No deaths occurred during treatment and clinical observations did not reveal any local alterations, but muscular clonus lasting for some minutes after administration was observed in the dogs treated with 40 and 80 mg/kg/day. This latter effect was not seen in the acute toxicity studies. Gross and histological examinations showed only slight modifications to the injection site in treated dogs compared with controls. The modifications were subacute periphlebitis and occasional phlebitis, and these were more apparent in treated, than control dogs.

IM study with teicoplanin in saline (Oct 1982).

Teicoplanin in NaCl solution was injected at the concentration of 50 mg/kg. The solution was given at doses of 5, 20 and 40 mg/kg using one male and one female beagle dog for each dose. The dogs were treated with intramuscular injections of teicoplanin to the right thigh over a period of 2 weeks for a total of 7 treatments. At the time of the 7th injection in the right thigh, a single injection was also given into the left thigh, making possible the evaluation of local tolerance following both single and repeated administration. Gross and histological examinations were performed on all animals.

Gross examination revealed a lighter than normal appearance of the muscle with oedema or connective tissue proliferation in the 20 mg/kg male and in both 40 mg/kg dogs after repeated injections. Slight intramuscular or subcutaneous oedema was also observed following a single injection of 40 mg/kg. Histological examination revealed moderate subacute myositis after repeated injections in all the dogs given 20 and 40 mg/kg, and after a single injection in the female given 40 mg/kg. Little or no damage was seen in controls, 5 mg/kg dosed, or single injection 20 mg/kg animals.

IM study with teicoplanin in human albumin or povidone (Nov 1980).

Teicoplanin was administered IM to 1 mongrel dog/sex/dose. Teicoplanin was dissolved at a concentration of 25 mg/mL in 0.5% human albumin or 2.5% povidone. Each formulation was tested at doses of 5 and 30 mg/kg in volumes of 0.2 and 1.2 mL/kg respectively. One dose of either formulation was injected twice into the same animal, first into the right thigh and after 5 days into the left. All dogs were killed 2 days after the second injection and subjected to examination.

Clinical symptoms, consisting of limping on the leg into which the injection had been given for a few hours after the injection, was observed in two animals given 30 mg/kg teicoplanin in human albumin solution. At autopsy, subcutaneous haemorrhages were noted in the thigh area in an equal number of dogs of both doses (5 and 30 mg/kg) for both vehicles. Histological examination of the injection sites revealed signs of inflammation which were less obvious in the povidone (5 mg/kg) formulation group than the human albumin (5 mg/kg) formulation group. In the groups given 30 mg/kg teicoplanin, there were signs of degeneration and inflammation (foci of necrosis of muscle fibres), which on the whole were more extensive in the animals given teicoplanin in 0.5% albumin than in the other vehicle, povidone. There were no saline (untreated) controls used in this study, so the only reliable information gained was the relative effects of either vehicle solution.

5.2.2 Rats

IM or SC study with teicoplanin in sodium deoxyribonucleic, dextran 40.000 or human albumin (Feb 1980).

Local tolerance studies in the male Sprague Dawley rat with teicoplanin dissolved in sodium deoxyribonucleic, dextran 40.000 or human albumin, given by either IM or SC routes were conducted. Teicoplanin was dissolved at a concentration of 25 mg/kg in the three solvents of the following strengths, 0.23% sodium deoxyribonucleic, 5% dextran 40.000 or 0.5% human albumin. Animals were subdivided into 3 groups of 5 each. Each group was given teicoplanin dissolved in a different solvent at a concentration of 25 mg/mL. Every animal was given two treatments at the same site, with a 24-hour interval between the two treatments. The volume injected was 0.2 mL/injection. The animals were sacrificed 24 hours after the 2nd treatment, and the injection sites were examined.

The treatment by intramuscular route with the 3 types of teicoplanin solutions caused local lesions of the inflammatory type, some hyperaemia and moderate bleeding, and degenerative changes in the muscle tissue. Of the three vehicles tested, the human albumin solution was the least damaging. After SC treatment, teicoplanin dissolved in the three different solvents exerted slight irritating local effects of inflammatory type exclusively, manifested by hyperaemia and moderate bleeding in some of the animals. The three solvents were given alone by both the routes used in this study and they had minimal irritating effects (hyperaemia) in a few animals.

5.2.3 Rabbits

IM study with teicoplanin in povidone or human albumin (May 1980)

This study looked at the local tolerance of teicoplanin dissolved at a concentration of 25 mg/mL in 2 different solvents: a 2.5% aqueous solutions of povidone and a 0.5% aqueous solution of human albumin. Animals were subdivided into 6 groups of 2 rabbits each, and each group was treated with one of the following: povidone, teicoplanin + povidone, human albumin + teicoplanin, saline or distilled water. The sacrospinal muscles were the injection sites in all the animals, the left one was treated 7 days before sacrifice, the right one 2 days before. One mL of solution was injected into a single site in each of the muscles.

The occurrence of bleeding was at a moderate level in teicoplanin and vehicle control groups, but only at a trace level (or none) for saline or distilled water injection. Degeneration at the injection site in the two groups treated with teicoplanin was more evident than seen in all four control groups. Necrosis, at the injection site was only observed in two animals, one rabbit in the teicoplanin + human albumin group (slight degree) and a rabbit from the distilled water control (trace level) group. Of the two vehicles used for the formulation of teicoplanin in solution, povidone was tolerated to a better degree than human albumin.

6 REPEAT DOSE TOXICITY

The following repeat-dose toxicity studies were performed at G. Lepetit Research Laboratories (Italy) and complied with GLP.

6.1 Rat Studies

6.1.1 One month IV study (Oct 1981).

A toxicity study was conducted in five groups of CD Sprague Dawley rats (10/sex/group) which were given teicoplanin (in saline) by the IV route at dose levels of 0, 10, 20, 40 and 80 mg/kg/day for one month (31-32 days).

Plasma levels of teicoplanin and/or active compounds were determined by microbiological assay at various times during treatment. The results are summarised in section 4.1.1.

There were no treatment-related deaths during the study. Clinical signs included slight and transient reductions in spontaneous activity lasting 30 min to 1 h after administration (10 and 20 mg/kg/day), and slight ataxia and dyspnoea in some animals given 20 mg/kg/day (1st day only). From the 10th day through to the end of the study, no symptoms were observed in the two low dose groups (10 and 20 mg/kg). Administration of the higher doses (40 and 80 mg/kg/day) were followed by marked sedation (40 mg/kg) and prostration (80 mg/kg), ataxia and dyspnoea. At the 80 mg/kg dose, and only for the first 4 days, there was an intense reddening of the skin. On continuation of treatment, progressive reductions in the intensity and duration of the behavioural changes were observed.

Food consumption was generally unaffected by treatment, but slight reductions were seen in males (80 mg/kg) in week 1 (14%) and week 4 (9%). In all groups except males receiving 80 mg/kg, the bodyweights of the rats were comparable to that of the controls over the duration of the study.

Ophthalmic examination did not reveal any abnormal findings.

Urinalysis identified modifications to urinary parameters at the 40 and 80 mg/kg levels. Changes seen following treatment with teicoplanin (80 mg/kg) were: numerous sloughed cells of the lower urinary tracts and numerous granular casts in a majority of animals of both sexes, sloughed cells of the upper urinary tracts in 5/10 males and 3/10 females, and presence of haemoglobin and red blood cells in 3/10 males and 3/10 females. In the 40 mg/kg group, only rare granular casts were observed in 3/10 males and 6/10 females.

Blood chemistry parameters were not greatly changed by treatment with teicoplanin, but total protein was decreased by about 10% in both males and females at virtually all doses, as shown in the table:

	Total protein (g/dL)				
Group	**1**	**2**	**3**	**4**	**5**
Males	6.25	5.85	6.07	5.89	5.76
Females	6.61	5.85	6.02	5.77	6.05

While the total protein levels fell, the A/G ratio increased (dose-related) slightly in response to an increase in albumin levels and a decrease in the globulin fractions. The blood glucose concentration was significant elevated in females receiving 80 mg/kg (12%), however, the glucose level was not significantly elevated at any other dose level in females, nor in males.

Haematological parameters were not altered in male rats. However, in female rats, treatment-related changes appeared to be a reduction in PCV, RBC and haemoglobin at all doses. The magnitude of the change for each parameter was slight, and may not be of biological significance. The maximum change for each parameter was 8% (PCV), 9% (haemoglobin) and 12% (RBC), and the maximum change did not always occur at the highest dose.

Organ weight changes that appeared to be in response to treatment were found to occur mainly in female rats. Absolute adrenal weights increased at 10 (11%), 20 (15%), 40 (28%) and 80 (38%) mg/kg in females only, and a dose-related increase in the relative weight was also seen. The absolute and relative liver and ovary weights were significantly elevated by 43% and 17% respectively in females receiving 80 mg/kg teicoplanin. The absolute and relative weight of the kidneys of both sexes were significantly increased at the 20 mg/kg dose level and above. However, observed changes did not follow a dose-related pattern. The spleen of females showed dose-related increases in both absolute and relative weight, with a maximum increase of 38% (absolute) at 80 mg/kg.

Gross pathological examination led to findings of lighter than normal colour of the kidneys in 3 males (40 mg/kg) and in 8 rats/sex of the 80 mg/kg dose. There was a slight reduction of the cavitary adipose tissues in 8 rats/sex at the 80 mg/kg dose. Slight subcutaneous haemorrhagic suffusions were observed at the tail at the injection sites in all treated animals and controls. Histological examination revealed the presence of degenerative-necrotic aspects of the cortical tubular epithelia of the kidney; this was slight in 2 males and 1 female of the 40 mg/kg group, and slight to moderate in all the rats of the 80 mg/kg group. Also seen in the high dose group were hyaline casts or proteinaceous material in the lumen of the tubules. There was slight to moderate cytoplasmic vacuolization of the acinar epithelia of the pancreas. This effect was observed from 20 mg/kg, and was dose-dependent in frequency.

6.1.2 First one month SC study (July 1981).

A one month toxicity study was conducted in CD Sprague Dawley rats (10/sex/group) given teicoplanin at dose levels of 0, 25, 50, 100 and 150 mg/kg/day by the SC route.

Plasma levels of teicoplanin and/or active compounds were determined by microbiological assay at various times during treatment. The results are summarised in section 4.1.1.

During the study two females at the 150 mg/kg dose level died and two males were sacrificed in a moribund condition in the last week of the study. There were no adverse clinical signs in the groups treated with 25 and 50 mg/kg teicoplanin. In the animals from the groups receiving 100 and 150 mg/kg, there was evidence of reduced spontaneous activity, intermittent ataxia (150 mg/kg) and pilo-erection. Dose-related alopecia and/or a few small crusts or eschars at the injection sites were observed starting from the 5th to 6th day in all the animals at the 150 mg/kg dose level and in lower dose groups (50 and 100 mg/kg).

Food consumption of both sexes was not affected by dosing with 25 and 50 mg/kg teicoplanin, and for the females of the 100 mg/kg group. Males receiving 100 mg/kg teicoplanin consumed 17% less food in week 1 and 21% less in week 4. Females receiving 150 mg/kg showed a 20% reduction in food consumption in week 4, but males receiving this dose showed a reduction in food consumption in each week ranging from 20% (week 1) to 54% (week 4). Water consumption was variable, but unaffected by treatment. Bodyweight of both sexes was not affected by treatment with 25 and 50 mg/kg teicoplanin when compared with controls. At 100 mg/kg teicoplanin there was a 17% reduction in bodyweight (week 4) of males, but no change in females. At 150 mg/kg teicoplanin, females registered a bodyweight reduction of 11% only at week 4, while males showed a reduction from week 1, which culminated in a weight loss of 32% (compared with controls) by the end of week 4.

Ophthalmic examination was generally clear except for one male (150 mg/kg group) with a small area of posterior opacity of the lens of one eye.

Urinalysis revealed the presence of variable quantities of haemoglobin and red blood cells in 50% of males in group 4 (100 mg/kg), and in all the males and 50% of the females in group 5 (150 mg/kg). Proteinuria was increased in male and female rats from group 5 (150 mg/mL). Six males and two females registered levels of 100 mg/dL protein, while no animals in any other group (1 to 4) had above 30 mg/dL protein in their urine. Kidney damage was evident since there were numerous flaked cells of the upper and lower urinary tracts, granular casts and increased numbers of leukocytes found in the sediment from treated animals. These cells were found in a majority of animals (both sexes) in the 150 mg/kg group, and to a lesser extent in the 100 mg/kg group.

Clinical chemistry analysis in males revealed the presence of treatment related changes starting at 100 mg/kg teicoplanin. The only variation from this trend was total protein concentration which was found to be reduced at 50 mg/kg (13%) as well as at 100 mg/kg (17%) and 150 mg/kg (19%). Blood glucose concentrations fell at 100 mg/kg (18%) and 150 mg/kg (13%), and BUN levels were markedly elevated (166%) only at 150 mg/kg. Other parameters to show significant variation (only at a dose of 150 mg/kg) were SGPT (increased 46%) and serum AP (decreased 52%).

The effect of teicoplanin treatment on clinical chemistry parameters in females was less dramatic than that seen in males. BUN levels were elevated by 62% (150 mg/kg), SAP levels were reduced by 44% (150 mg/kg), and total protein concentrations showed a dose-related reduction starting at 50 mg/kg (10%), with a maximum fall of 15% at 150 mg/kg.

Haematological examination was unremarkable except for white blood cell number and the differential count. The increase in white blood cell count appeared dose-related in nature:

WBC ($10^3/mm^3$)

Group	1	2	3	4	5
Males	12.7	14.5	17.8	20.2	20.0
Females	12.6	12.7	13.6	19.1	18.6

There was a shift in differential white cell count, with a dose-related increase in neutrophils and a concomitant reduction in lymphocytes.

Organ weight analysis was complex when the weight loss suffered by animals in the high dose group was taken into account. The absolute liver weight was significantly down in males of group 5 (150 mg/kg), but the relative weight was not. The reduction in absolute liver weight may be in response to the drastic body weight loss suffered by the group 5 (150 mg/kg) males.

Both the absolute and relative liver weights were significantly increased in females from all treatment groups (not dose-related). The relative kidney weight in males showed a dose-related increase which reached 76% at 150 mg/kg, while the absolute weight fluctuated over the dose range. Both the absolute and relative weight of kidneys in females were greater than control values at all doses. At 150 mg/kg the absolute weight was 19% greater than control, and the relative weight was 47% greater than the control kidney weights in females. The relative and absolute weight of the spleen was increased in females at all doses, and in males up to the 100 mg/kg dose, while a reduction of the absolute weight, and an increase of the relative weight was observed in the 150 mg/kg males. The adrenals of females receiving 150 mg/kg teicoplanin showed a marked increase in the absolute (35%) and relative (71%) weight.

Necroscopic examination revealed treatment-related alterations in the physical condition of the rats. Atrophy of the thymus in males (6/10) at the 100 mg/kg dose, and in both males (8/8) and females (4/8) of the 150 mg/kg group. Mild hypertrophy of the adrenal glands was seen in 3/8 females of the 150 mg/kg group.

There was evidence of proliferation of the subcutaneous connective tissue, sometimes associated with haemorrhagic punctata or suffusions, at the sites of injection in all rats treated with teicoplanin. The grading of this change appeared dose-related, with some rats in the high dose groups showing focal necrotic lesions of the subcutaneous tissue. Macroscopic evidence of nephritis and/or nephrosis were found in the following frequency:

Group	1	2	3	4	5
Males	5/10	5/10	10/10	10/10	8/8
Females	1/10	0/10	0/10	3/10	7/8

Histological examination was carried out in all control and group 5 (150 mg/kg) rats. Examination of organs presenting lesions in the 150 mg/kg group was also carried out for lower dose groups. Cytoplasmic vacuolization of the epithelia of the pancreatic acini was identified in nearly all animals treated with teicoplanin. Frequencies of this lesion are shown in the following table:

Group	1	2	3	4	5
Males	1/10	10/10	10/10	9/10	8/8
Females	0/10	8/10	10/10	9/10	8/8

The degree of vacuolization was described as slight to mild in females in the lower dose groups, and moderate to marked in all other cases.

Atrophy of the thymus was confirmed by histology in 1/10 males of the 100 mg/kg group and in 8/8 males and 5/8 females of the 150 mg/kg group.

There was an increase of neutrophilic granulocytic elements and, sporadically, also of the eosinophilic ones of the bone marrow, in 1/5 males of the 25 mg/kg group, 1/5 females of the 50 mg/kg group, 4/5 males and 3/5 females of the 100 mg/kg group, and 5/5 males and 5/5 females of the 150 mg/kg group. Also, a slight hypertrophy and cytoplasmic vacuolization of the epithelium of some follicles with reduced lumen of the thyroid was seen in 1/3 males of the 100 mg/kg group and in 2/8 males of the 150 mg/kg group.

Kidney damage was evident in all groups examined, including controls. Types of lesions were subacute interstitial nephritis and/or nephrosis, and were seen at the following intensity and frequency:

Animals with renal lesions

Dose	Slight to moderate		Marked	
(mg/kg)	Male	Female	Male	Female
0	8/10	8/10	2/10	0/10
25	7/10	6/10	3/10	0/10
50	4/10	6/10	6/10	0/10
100	2/10	6/10	8/10	0/10
150	0/8	8/8	8/8	0/8

The intensity of the lesions appeared to be greatest in males treated with 50 mg/kg or above.

6.1.3 Second one month SC study (Feb 1983).

A four week toxicity study was conducted after administration of teicoplanin to rats by the SC route. Five groups of CD Sprague Dawley rats (10/sex/group) were given teicoplanin (in saline) at doses of 0, 10, 20, 50 and 150 mg/kg/day for 4 weeks (29 to 31 days).

One male rat from the 50 mg/kg group died on day 13 of the study, but autopsy did not reveal the cause of death. Clinical signs related to treatment were not detectable at 10 and 20 mg/kg. At the higher doses of 50 and 150 mg/kg teicoplanin, there was injection site damage characterised by thickening of the skin, alopecia and skin lesions. Food consumption was not adversely affected by doses of 10, 20 and 50 mg/kg teicoplanin, but at the highest dose of 150 mg/kg, there was a 17% reduction in food consumption at the 4th week in males, and a 20% reduction at the first week in females, before recovering to a normal intake. As a result, the body weight of males in the 150 mg/kg group was 13% below the control weight, and the body weight of females in the 150 mg/kg group showed a transient reduction of 5% (week 1) before recovering to control levels. There were no effects on body weight in other groups.

Ophthalmic examination of all groups was unremarkable.

Urinalysis revealed a few upper urinary tract epithelial cells and many granular casts in the sediment of all animals at 150 mg/kg. A few granular casts were also noticed in 2/10 males and in 9/10 females at 50 mg/kg. A small number of erythrocytes and small amounts of haemoglobin were found in all males and 9/10 females at the 150 mg/kg level.

Clinical chemistry evaluation revealed a dose-related reduction in total proteins in both sexes:

Total Proteins (g/dL)

Group	**1**	**2**	**3**	**4**	**5**
Males	6.14	5.57	5.72	5.41	5.16
Females	6.60	6.44	6.16	5.61	5.36

Other variations from control were only seen in the rats treated with 150 mg/kg teicoplanin. These changes were a significant increase of SGPT in both males (30%) and females (36%), a significant elevation in the concentration of BUN in males only (16%), a decrease in the alkaline phosphatase levels in males (40%) and females (28%), and a decrease in the albumin/globulin ratio following an increase in globulin and a decrease in albumin levels.

Haematological evaluation of the groups was unremarkable except for the number of circulating leukocytes and the differential count. The white cell count for the groups at the 4th week is shown in the table:

Group	1	WBC ($10^3/mm^3$) 2	3	4	5
Males	13.5	14.8	15.4	18.4	24.8
Females	10.4	11.0	12.8	13.9	16.9

The changes in WBC in group 5 at the 4th week represents an 84% increase in males and a 63% increase in females. Associated with this change was a moderate increase in neutrophils and a decrease in lymphocytes in the differential count in both sexes treated with 150 mg/kg teicoplanin.

At necropsy the macroscopic findings related to treatment with teicoplanin were: kidneys of a pale colour in males (7/10) and females from group 5 and in one male from group 4 (50 mg/kg); enlargement of the spleen in male (5/10) and female (2/10) rats receiving 150 mg/kg teicoplanin and in 2 male rats from the 50 mg/kg group; injection site damage in the 50 and 150 mg/kg group (both sexes). A deterioration of general body condition of almost all rats from the 150 mg/kg group and one female of the 50 mg/kg dose level was also observed.

Organ weight changes were recorded for the spleen, liver and kidney. A dose-dependent increase in the absolute weight of the spleen was noted for both sexes. At the highest dose level (150 mg/kg) the spleen weight had increased by 49% in males and 69% in females. Slight increases of the absolute kidney weight were noted for females receiving 50 mg/kg (14%) and 150 mg/kg (16%). The absolute liver weight of females dosed with 150 mg/kg increased by 18% over the control weight by the end of the dosing period.

Histological examination revealed changes in the kidney which were characterised by cortical tubular epithelial degeneration in all animals receiving 150 mg/kg and in one female receiving 50 mg/kg, while one male receiving 150 mg/kg showed a slight steatosis of the cortical tubular epithelium. Pancreatic cytoplasmic vacuolization of the acinar cells in all treated animals was graded as severe in the 50 and 150 mg/kg groups, moderate at the 20 mg/kg level, and slight at the 10 mg/kg level. Skin at the injection site showed signs of necrotizing inflammation which was moderate to severe in all rats treated with 20, 50 and 150 mg/kg teicoplanin. The spleen showed slight to moderate reactive inflammation and haematopoiesis in all the control and treated groups; these modifications appeared comparable in controls and rats receiving 10 mg/kg teicoplanin, but were more apparent at higher treatment doses. An incidence of very slight to moderate hypertrophy of the follicular epithelium of the thyroid was detected in all treatment groups and to a lesser degree in control rats.

6.1.4 Six month treatment, 9 week recovery SC study (Jan 1984).

Four groups of CD Sprague Dawley rats (26/sex/group) were given teicoplanin (in saline) by the SC route at dose levels of 0, 5, 10 and 30 mg/kg/day respectively, for 26 weeks. An interim sacrifice of 5 rats/sex/group was performed after 13 weeks of treatment. When teicoplanin treatment was terminated, 6 rats/sex/group were kept untreated for an additional 9 week period for recovery studies and all other rats were sacrificed for necropsy.

Plasma levels of teicoplanin and/or active compounds were determined by microbiological assay at various times during treatment. The results are summarised in section 4.1.1.

Four rats died during the study, two males (days 66 and 98) and one female (day 242) from the group receiving 30 mg/kg teicoplanin, and one male (day 184) from the group receiving 5 mg/kg teicoplanin.

Observable clinical signs during the treatment and recovery periods were almost entirely confined to injection site damage (alopecia, epidermal crusts, thickening of the skin, palpable subcutaneous thickening), and, although these signs were evident in control animals, there was a dose-related increase in intensity of these effects in treated animals.

Food consumption for both sexes was not adversely affected by teicoplanin treatment. There were sporadic instances of increased food consumption by both sexes, but these followed no set pattern and were of no biological significance.

Body weight gain of males receiving 5 and 10 mg/kg, and females receiving 5 mg/kg teicoplanin was comparable to the gain seen in control animals over the duration of the study. Males receiving 30 mg/kg teicoplanin had bodyweight gains comparable with control animals up to week 8 of the study, after which time there was a decrease in bodyweight gain that continued to the end of treatment. Recovery of bodyweight in this group of males (30 mg/kg) was complete by the 8th week after withdrawal of treatment. Females receiving 10 and 30 mg/kg teicoplanin displayed reduced bodyweight gain when compared with controls from weeks 12 and 8 of treatment, respectively. The change in these groups (10 and 30 mg/kg) was a slight growth retardation of an approximate maximum of 15% for either group, which persisted to the end of the treatment and recovery (withdrawal) phases.

Urinalysis was generally unremarkable except for the detection of granular casts in the sediment of all the animals at 30 mg/kg (both sexes). The frequency of appearance of the granular casts varied from a few at 3 months to moderate amounts at 6 months. A few granular casts were also noticed after 6 months in 2/10 females at 10 mg/kg. No changes (casts) were found after the recovery period.

Haematological evaluation revealed a slight decrease of the PCV and Hb values (10% in all instances) for both sexes at 30 mg/kg, and an increase (dose-related) in the WBC count in males of up to 90% (30 mg/kg) at 3 months and 51% (30 mg/kg) at 6 months. The change in WBC for females was not marked at 3 months, but at 6 months an 81% increase was recorded at a dose of 30 mg/kg. The trend toward an increased WBC counts was reversed in both sexes during the withdrawal period. The changes in the WBC were accompanied by a moderate increase in neutrophils, associated with a concomitant decrease of lymphocytes in the differential count.

Blood chemistry analysis revealed a decrease in the total proteins in both sexes at all dose levels after 3 and 6 months of treatment. The maximum reductions in total proteins (13-15%) was always seen at the highest dose regardless of sex. There was a complete recovery to control levels of total protein (small overshoot in some instances) by the end of the withdrawal period. Gamma globulins were decreased in all treated groups for both sexes after 3 months, and for females after 6 months. Slight decreases of albumin (12%) and AG ratio (20%) for males at 30 mg/kg after 3 months were observed.

Incidental changes in BUN and glucose levels were variable over time (3 or 6 months), and lacked dose-relationships. Serum AP was down at 3 month (all doses) in females, but normal at 6 months (all doses). In males treated with 30 mg/kg, SAP levels were 29% below control levels at 6 months, but no differences were seen at all other treatment levels.

The findings at necropsy included pale kidneys in approximately 80% of rats receiving 30 mg/kg and in approximately 30% receiving 10 mg/kg at both the 3 and 6 month sacrifice. There was also a slight increase in volume of kidneys in approximately 30% of rats receiving 30 mg/kg teicoplanin at 6 months. At 3 months, both higher dose groups (10 and 30 mg/kg) had instances (20-40%) of increased kidney volume. Injection site damage was characterised by ecchymoses or darker zones, zonal rarefactions of the hair, alopecia and skin encrustations, which were slight to moderate in several animals of the 5 and 10 mg/kg groups, and slight to severe in all the 30 mg/kg treated rats sacrificed after 3 or 6 months. Similar signs of injection site damage were also observed in control animals, but to a minimal extent. An increase in the volume of the spleen was observed as slight in some animals (7/39) of the 5 mg/kg group, and slight to moderate in numerous 10 (23/40) and 30 (29/38) mg/kg treated animals sacrificed after 3 or 6 months. Uterine horn dilatation with fluid in the lumen was observed in females of all treatment groups (not controls) at both 3 and 6 month sacrifices. The frequency of occurrence of this change was low (20%) and did not follow a dose relationship. A slight increase in the volume of adrenals of females in groups receiving 5 (2/15), 10 (1/15) and 30 (8/15) mg/kg was observed at 6 months.

Examination of animals sacrificed at the end of the recovery period revealed a reduction in the severity of the effects described above.

The following significant changes in relative organ weights (as a percentage of the control value) were noted:

Dose		**5 mg/kg**	**10 mg/kg**	**30 mg/kg**
			% change at 3 months	
Males	Liver	+36	+25	+31
	kidneys	+18	+14	+33
	spleen	+43	+46	+124
	gonads	+12		+21
Females	Liver	+18		+18
	kidneys	+21	+18	+44
	spleen	+33	+54	+61
	adrenals	+32	+26	+58
	uterus	+12	+16	+80

		% change at 6 months		
Males	Liver			-8
	kidneys			+24
	spleen	+26	+56	+85
	adrenals	+25	+38	+75
	gonads			+26
Females	Liver	+16	+22	+35
	kidneys	+21	+34	+59
	spleen	+33	+48	+92
	adrenals	+22	+28	+72
	uterus	+31	+67	+185

In all instances, the relative organ weight changes observed at 3 and 6 months were less obvious at the end of the recovery period.

The histological findings showed slight nephropathy in all treated animals (5/sex/group) killed at 3 months, but in no controls. At 6 months however, nephropathy was found in 5/20 controls, 4/20 LD, 2/20 MD and 0 HD rats, suggesting tolerance may have developed. Tubular dilatation was found in 11/20 controls and 20/20 rats in all other groups at 6 months. Cytoplasmic vacuolization of pancreatic acinar cells was observed in all groups (including controls) at 3 and 6 months, and the frequency and severity of this lesion were dose-related. Injection site damage was characterised by subchronic inflammation of cutaneous/subcutaneous tissue, epidermal erosion and thickening, hair follicle decrease, degeneration of fibers and chronic inflammation of muscles. All of these changes were seen in all treatment animals at 3 and 6 months, except for skin thickening and hair follicle decrease (seen at 10 and 30 mg/kg) and degenerative changes (seen at 30 mg/kg at 6 month only).

A slight to moderate reactive inflammation and haematopoiesis of the spleen was observed in all groups, including controls. The severity of this response was comparable in the control, low (5 mg/kg) and medium (10 mg/kg) dose groups, but was more evident in rats given 30 mg/kg at both 3 and 6 month examinations. Minimal to moderate hypertrophy of the follicular epithelium of the thyroid was observed in all groups at both the 3 and 6 months sacrifice, with the changes seen in controls being of a lesser degree. Endometrial inflammation was observed in all treated females at the 3 and 6 month sacrifice, and while this reaction was also seen in control rats, it was less severe than the inflammation seen in treated animals.

Other changes that occurred to a greater extent in animals treated with 30 mg/kg teicoplanin than in other groups were increased vacuolation of cortical epithelia of the adrenals (6 month), slight increases in liver steatosis (6 month), and an increase in the basophilic cells of the pituitary (6 month).

Histiocytic infiltrations were noticed in various organs (all animals) and were considered a specific reaction to the prolonged and often severe injection site irritation.

At the end of the recovery period the findings from histological examination revealed an apparent reversibility of the treatment related changes.

In summary, the changes observed in clinical chemistry parameters were not indicative of prominent toxic effects resulting from the administration of teicoplanin. There were no signs of necrotic (organs) changes, but there was evidence of a toxicity (steatosis, vacuolation, hypertrophy), which was dose-related. The observable toxicity was not severe and was reversible at the doses used in this study.

6.1.5 One month oral study

A toxicity study was conducted in five groups of CD Sprague Dawley rats (10/sex/group) given teicoplanin by gavage at dose levels of 0, 200, 400, 800 and 1200 mg/kg/day for 1 month. The following examinations were performed at the end of the study: ophthalmoscopy, urinalysis, blood chemistry, haematology, necropsy, organ weights and histology.

Plasma levels of teicoplanin and/or active compounds were determined by microbiological assay at various times during treatment. The results are summarised in section 4.1.1. No drug related compounds were detectable at the 200, 400 or 800 mg/kg doses, but measurable amounts were found in males only at 6 hours after the first (1.54 μg eq/mL) and 8th (0.76 μg eq/mL) treatment following the 1200 mg/kg dose.

The only drug- and dose-related changes were slight increases of water consumption at all dose levels, and associated dilatation with repletion of the caecum and colon at highest dose level in both sexes. There were no other effects that could be associated with treatment.

6.1.6 8 day SC nephrotoxicity study (Dec 1980).

A study comparing the nephrotoxic effects of teicoplanin (SC) with vancomycin (SC) was conducted in Sprague Dawley rats. Groups of Sprague Dawley rats (10/sex/group) were given teicoplanin at doses of 25, 50 and 100 mg/kg, or vancomycin (used as a reference compound) at doses of 100 and 500 mg/kg, once daily for 8 consecutive days. An untreated control was included in the schedule. The dosages were chosen on the basis of results from comparative <u>in vivo</u> mouse infection studies.

There were no deaths recorded during this study. Bodyweight gain over the 8 days of the study was reduced from between 30 to 50% in both sexes of both the teicoplanin and vancomycin high dose groups. All other groups had bodyweight gains comparable to controls. Water consumption was comparable for all groups in the study.

Urinalysis included measurement of the activity of alkaline phosphatase (AP), lactic dehydrogenase (LDH) and leucine aminopeptidase (LAP). The effect of both antibiotics on the activity of these enzymes was variable. In male rats the administration of teicoplanin (100 mg/kg) led to an increase in AP, LAP and LDH of between 25 to 60% above control levels, while the two lower doses (25 and 50 mg/kg) did not cause a significant change in enzymes levels. A similar trend was seen in female rats treated with teicoplanin. Vancomycin at the lower dose (100 mg/kg) had no effect on the enzyme levels in either male or female rats. However, in males treated with the high dose of vancomycin (500 mg/kg) the levels of AP, LAP and LDH were significantly below control levels. The higher dose (500 mg/kg) of vancomycin in females caused the AP levels to increase (600%), LDH levels to fall (15%) and LAP levels to rise (30%). No modifications of statistical or biological significance were detected with regard to the remaining parameters measured during urinalysis.

Clinical chemistry evaluation carried out at the end of the study was generally unremarkable except for total protein concentrations, which fell slightly in all treatment groups for both antibiotics. The maximum reductions in total proteins were 9% in females and 13% in males. Creatinine clearance was found to be unaffected by either antibiotic.

Gross examination at sacrifice revealed injection site damage, characterised by subcutaneous necrosis and haemorrhagic punctata, mild hyperaemic areas and slight or mild foci of subcutaneous connectivization, in both the teicoplanin and vancomycin groups. The severity of lesions was dose-dependent. There was no gross evidence of renal damage: the absolute and relative kidney weights from all groups were similar.

Histological examination of the kidneys from rats treated with teicoplanin (50 and 100 mg/kg/day) or vancomycin (100 and 500 mg/kg/day) revealed an increase in frequency and/or intensity of degenerative aspects of the cortical tubular epithelia, sometimes associated with fibrohistiocytic interstitial reaction, or with the presence of rare hyaline casts. These lesions were seen in 2/20 controls, 1/20 LD, 6/20 MD and 7/20 HD teicoplanin-treated rats, and in 7/20 LD and 8/20 HD vancomycin-treated rats. The severity of the lesion was greatest in the HD vancomycin group. In addition, slight dilatation of the lumen of some cortical tubules, sporadically with hypotrophy of the epithelia, was observed in 1/20 MD and 2/20 HD teicoplanin-treated rats, and 5/20 LD and 8/20 HD vancomycin-treated rats. There were no other treatment related modifications in the kidneys.

Overall, it would appear that treatment with teicoplanin at 25 mg/kg/day for 8 days did not cause any functional or morphological aberration to the kidneys. At higher doses, teicoplanin has renal toxic effects which are similar to those produced by vancomycin.

6.2 Dog Studies

6.2.1 One month IV study (Nov 1981).

Five groups of beagle dogs (2/sex/group) were treated IV with doses of 0, 5, 10, 20 and 40 mg/kg/day of teicoplanin (in sterile distilled water), 7 days a week for 4 weeks. Plasma levels of teicoplanin and/or active compounds were determined by microbiological assay at various times during treatment. The results are summarised in section 4.3.1.

No deaths occurred during the study. There were no apparent treatment related affects on animal behaviour (clinical signs), food and water consumption, bodyweight, ophalmoscopic examination, haematology evaluation, and organ weight analysis.

Urinalysis revealed the presence of granular casts and sloughed cells of the upper urinary tract in a moderate quantity, sloughed cells of the lower urinary tract, haemoglobin and red blood cells in notable quantities in urine from one male from the 40 mg/kg, and haemoglobin and cells in notable quantities in urine from one female of the 40 mg/kg group.

Blood chemistry examination was generally unremarkable except for one male (40 mg/kg group) that had a lowered A/G ratio as a result of reduced albumin and increase globulin concentrations.

Findings at autopsy were: lighter than normal appearance of kidneys in 1 male and 1 female of the 40 mg/kg group; lighter than normal appearance of liver in 1 male from the 40/kg group; injection site proliferation of connective tissue around the veins were slightly more intense than in the controls, this effect was seen in 1 male from the 20 mg/kg group and in 2 males and 1 female from the 40 mg/kg group.

Histological examination revealed slight and mild degenerative aspects (kidney) of the epithelium of the cortical tubules in the 40 mg/kg males. Slight steatosis of the liver in the 40 mg/kg females. Injection site damage was related to moderate aspects of phlebitis and periphlebitis found to be slightly more intense in treated animals than controls.

6.2.2 One month IM study (Feb 1981).

Five groups of beagle dogs (2/sex/group) were treated IM with doses of 0 (saline), 5, 10, 20, and 40 mg/kg/day of teicoplanin, 7 days a week for 4 weeks. The saline control had povidone added since this was the vehicle for teicoplanin. Plasma levels of teicoplanin and/or active compounds were determined by microbiological assay at various times during treatment. The results are summarised in section 4.3.1.

There were no deaths, food and water consumption was similar for all groups, and body weight analysis and ophthalmic examination were both unremarkable. Clinical observations revealed some transient signs, mainly consisting of redness of the skin, itching, congestion of conjunctiva, piloerection, and in one dog (40 mg/kg group), a papular reaction. These clinical observations were not prominent at the 5 mg/kg teicoplanin level, but were seen at the higher doses. In one animal at 40 mg/kg teicoplanin there were episodes of local tremor, vomiting and sedation, but these were transient. The control group given the vehicle (povidone, 2.5%) also displayed clinical signs similar to those observed in the treated animals.

Detailed analysis of the condition of the animals involved examination of blood chemistry, haematology, urinalysis, organ weight, gross pathology at necropsy and histopathology. Treatment with teicoplanin, over the dose range of 5 to 40 mg/kg, had no effect on the parameters above, except in the histopathological examination. There were signs of mild renal toxicity characterised by hypotrophy of the epithelia and dilation of the lumina of some cortical tubules in one dog of each of the 20 and 40 mg/kg groups. There were signs of degenerative and inflammatory modifications at the injection sites which were more prominent in treated animals ($\geq$ 10 mg/kg) than controls.

6.2.3 Six month treatment, 10 week recovery IM study (Jan 1984).

Four groups, of beagle dogs (8/sex/group) were treated IM with daily doses of 0, 10, 20 and 40 mg/kg teicoplanin, respectively for 6 months. At 3 months an interim sacrifice of 2 male and 2 female dogs per group was carried out, and at the end of the 6 month treatment period 2 male and 2 female dogs per group were kept untreated for a 10 week recovery period. PLasma levels of teicoplanin and/or active compounds were determined by microbiological assay at various times during treatment. The results are summarised in section 4.3.1.

There were no recorded deaths in the 6 month dosing period or the 10 week recovery period. Clinical signs observed during the study were slight lameness (periodic) of the injected leg observed for a few hours in 3/16 control dogs, 1/16 from the 10 mg/kg group, 6/16 from the 20 mg/kg group and 11/16 dogs treated with 40 mg/kg. There were episodes of mucoid faeces (all groups) and sporadic vomiting in all groups. Although there was no pattern with regard to timing of the occurrence of vomiting, more animals in the high dose group vomited compared to the other groups. Slight to moderate sedation was observed for 3 days during the 4th month in dogs of the 40 mg/kg group. One female from the 40 mg/kg group displayed slight to moderate muscular tremors on the 110th and 111th day of the study.

No changes in food consumption of any treated group was noted, nor were there any abnormal findings during ophthalmic examination. There were no statistically significant treatment-related affects with regard to bodyweight gain of the dogs over the course of the dosing and recovery periods. The only change seen in the bodyweight gain assessment was a slight increase for all treated groups when compared to controls.

Clinical laboratory studies were in general unremarkable. Haematological evaluation did not reveal any treatment-related effects at either 3 or 6 months, or following the recovery period. Urinalysis revealed the presence of granular casts in the urine of animals from groups receiving 20 and 40 mg/kg (no quantitative data supplied). The appearance of granular casts was found to be reversible after the recovery period.

In blood chemistry, SGPT levels showed a slight to marked increase in both male and female dogs given 20 and 40 mg/kg at both 3 and 6 months (see table below).

SGPT (IU/L)

	At 3 months				At 6 months			
Dose	**0**	**10**	**20**	**40**	**0**	**10**	**20**	**40**
Male	34	35	36	95	66	55	85	167
Female	37	36	47	68	36	50	83	153

The levels of SGOT were increased in both sexes at 3 and 6 months for the higher dose groups (20 and 40 mg/kg), but the changes were within the normal biological range (documented). The changes in the levels of both SGPT and SGOT were showing signs of recovery by the end of the withdrawal period. Other parameters examined were within biological limits (documented).

Observation made at necropsy could be summarised as follows: pale kidneys, from slight to severe, which were dose related in dogs at the 6 month sacrifice, and less severe at 3 months. A slight increase in kidney volume was noticed in 3/8 dogs from the 40 mg/kg group at the 6 month sacrifice. There was an increase in the volume of the liver (slight to moderate), which was accompanied by a pale appearance, in all dogs receiving 40 mg/kg at the 6 months sacrifice. One female of the 20 mg/kg group also exhibited a pale liver at 6 months, while one female from the group receiving 40 mg/kg displayed a pale liver at the 3 month sacrifice. Modifications to the appearance of the liver, that were observed at 3 and 6 months, were not visible at the end of the recovery period.

Injection site irritation consisted of fibrosis of intermuscular connective tissue and multifocal pale areas of the muscle. The occurrence and intensity of these tissue changes were dose-related and were detectable at 3 and 6 months.

The frequency and intensity of tissue aberrations, noted during the treatment period, had significantly abated by the end of the recovery time.

Organ weight analysis revealed a complex array of changes in kidney and liver weights at the 3 month sacrifice. Both the kidney and liver weights showed marginal increases in males, but the direct opposite occurred in females (decreased), at 3 months. No other changes were detected at the 3 month sacrifice. At the 6 month sacrifice, the kidney and liver weights showed increases of between 12% and 23% in both sexes given 40 mg/kg teicoplanin. No other changes were observed except for the spleen which showed a marginal decrease (15%) in weight for both sexes given 40 mg/kg teicoplanin. A reversal of the trends observed at 3 and 6 months was evident at the end of the recovery period.

Histological examination led to the following findings; cortical tubular degenerative nephropathy of the kidney in all the dogs given 20 and 40 mg/kg teicoplanin, the intensity was slight to moderate after 3 months and possibly severe after 6 months treatment. Slight cortical tubular degeneration was also noticed in 2 dogs of the 10 mg/kg group sacrificed after 6 months. At the two highest doses, aspects of tubular epithelia regeneration were present. Hepatocellular hypertrophy of the liver was observed in 2 and 3 dogs (20 and 40 mg/kg respectively) sacrificed after 6 months of treatment. Injection site damage was characterised by muscle fiber degeneration, interstitial inflammation and histiocytic infiltration. These changes in tissue condition were noticed at the 3 and 6 month sacrifices, and the intensity of change was dose-related.

Modifications to the kidneys in the high dose animals, and the diffuse histiocytosis present in all treated groups, were much less severe at the end of the recovery period.

6.2.4 One month oral study (April 1981).

Five groups of beagle dogs (2/sex/group), were treated orally with doses of 0, 100, 200, 400 and 800 mg/kg/day of teicoplanin. The compound was given in gelatine capsules as a single daily administration, 7 days a week for 4 weeks. Plasma levels of teicoplanin and/or active compounds were determined by microbiological assay at various times during treatment. The results are summarised in section 4.3.1.

No deaths occurred during the study. Clinical observations, food and water consumption, body weight, ophthalmic examination, urinalysis, blood chemistry analysis, haematology, autopsy and histological examination all produced results for treated animals that were comparable with the controls.

6.3 Ototoxicity in the guinea-pig (Kresge hearing research laboratory, April 1982).

The potential of teicoplanin to cause ototoxicity was investigated in 12 female Dunkin-Hartley guinea pigs. Teicoplanin dissolved in povidone was administered SC at a dose of 25 mg/kg, 3 times a day for 28 days. Controls (n = 5) received vehicle. At the end of treatment phase, guinea-pigs were allowed a 14 day stabilisation period followed by an 8 day observation period.

The concentration of teicoplanin and/or active compounds from samples from a satellite group of 4 guinea-pigs was determined using a microbiological assay. Plasma drug levels were about 30 μg eq/mL at 4-8 h (Tmax) after a single dose of 25 mg/kg teicoplanin, 72 μg eq/mL at 4 h after the last dose of the study, and no drug (detection limit 7.2 μg eq/mL) was detected in the perilymph fluid after the first or last dose of teicoplanin (see also section 4.6).

The presence or absence of the preyer pinna reflex (twitch response to loud noise) was determined daily during treatment and again during the observation period. None of the guinea pigs lost their preyer pinna reflex. This reflex is a response to a loud sound and is an indication of auditory function, but it is not to be confused with hearing, as hearing is a perceptual process.

Auditory function was also determined electrophysiologically during the 8 day observation period after guinea-pigs were anaesthetised. The ability of the cochlear to generate AC potentials in response to sounds of various frequencies was not altered by treatment with teicoplanin. The ability of the auditory nerve to be activated by sounds (assessed by the N1 threshold) was also not altered by teicoplanin. In addition, there were no differences in the loss of cochlear hair cells between the animals treated with teicoplanin (2.5% hair cell loss) or vehicle (2.7% hair cell loss).

The potential ototoxicity of teicoplanin was also determined by investigating the influence of ethacrynic acid (40 mg/kg), a compound which enhances ototoxic effects of drugs with ototoxic properties, on the effects of teicoplanin. Female guinea-pigs (3/dose of teicoplanin) received a single SC dose of teicoplanin at 75 mg/kg, 150 mg/kg or 400 mg/kg followed 2 h later by a single injection of ethacrynic acid. Controls (3/group) received teicoplanin followed by saline. The maximum output of the AC cochlear potential was similar in all groups of animals, and did not differ from values obtained in other experiments using untreated controls. However, although the cochlear hair cell count was similar to that found in previous controls (about 3%) at the LD and MD of teicoplanin (with or without ethacrynic acid), at the 400 mg/kg dose, teicoplanin (followed by saline) was associated with a 10% loss in hair cells. The significance of this latter finding is unclear, but the results with teicoplanin 400 mg/kg followed by ethacrynic acid were not given.

It should be noted that the ototoxic effects of amikacin (≥ 93 mg/kg IP for 7 days) were detected in the preyer pinna reflex test and in tests of the ability of the cochlear to generate potentials in response to sounds in cats.

7 CARCINOGENICITY - No data presented

8 GENOTOXICITY

8.1 Histidine reversion in Salmonella typhimurium

Three separate studies were carried out to investigate the mutagenic activity of teicoplanin in the histidine reversion test in Salmonella typhimurium. Because Salmonella typhimurium (strains TA 98, 100, 1535, 1537 and 1538) is a gram-negative organism, teicoplanin can be effectively assessed by this system. All studies used positive controls, which were effective, and were carried out in the presence and absence of metabolic activation (± S9). The strains TA 100 and TA98 carried plasmids. In the first study, a dose range of 1 to 1000 μg/plate teicoplanin resulted in a 50% plating efficiency at the highest dose (1000 μg/plate), and no mutagenic effect. In the other studies, a dose range of 30 to 5000 μg/plate resulted in a 13% plating efficiency at the highest dose (5000 μg/plate), and no mutagenic activity.

8.2 Gene conversion test in Saccharomyces cerevisiae D4.

Two colony types of Saccharomyces cerevisiae D4 were used in this study, the tryptophan^{+} and the adenine^{+}. The tests were carried out using positive controls and in the presence and absence of metabolic activation (± S9). A dose range of 500 to 4000 μg/mL teicoplanin was used with no dramatic toxic affect on the culture (67% survival) and no mutagenic activity.

8.3 Point mutation test in Schizosaccharomyces pombe.

The yeast strain Schizosaccharomyces pombe was used to test for forward point mutation induced by teicoplanin. A positive control was used and the test was carried out in the presence and absence of metabolic activation. A concentration range of 250 to 2000 μg/mL teicoplanin was used in this study. The survival rate of the test cells was never less than 82% (+ S9), the positive control was effective (20 times increase above negative controls), and teicoplanin did not induce an increased in mutation above the level seen for the negative control.

9 REPRODUCTIVE TOXICOLOGY

9.1 Teratology Studies in the Rat

9.1.1 Preliminary fetal toxicity SC study (G. Lepetit, Jan 1982).

A dose-range finding study was carried out in pregnant female Sprague Dawley rats by administering teicoplanin SC to groups of 5 animals at doses of 0, 10, 25, 50, 100 and 150 mg/kg/day from day 6-15 of pregnancy. The antibiotic was given dissolved at the concentration of 25 mg/mL in 2.5% povidone.

The administration of teicoplanin was well tolerated both by the dams and the developing fetus. No signs of embryo- or fetotoxic actions were observed in any group, where parameters such as pre-implantation loss, post-implantation loss, resorptions and weight of fetuses were the same for all groups (including controls). Clinical signs were unremarkable, with local irritation at the injection site being the same for all groups. At the 100 and 150 mg/kg dose levels there was a marginal body weight gain suppression (10%) in the pregnant females.

9.1.2 Fetal toxicity SC study (G. Lepetit, Aug 1983).

Four groups of 35 CD Sprague Dawley female rats each were administered teicoplanin SC at dose levels of 0, 50, 100 and 200 mg/kg/day from day 6-15 of pregnancy. Twenty-five females/group were sacrificed on day 21 of pregnancy while the remaining 10 females/group were allowed to deliver and rear their young to weaning at 21 days post-partum.

No maternal deaths were recorded and no changes in behaviour were observed at any dose level. The injection sites of rats treated with teicoplanin showed signs of thickening of the skin, areas of alopecia and/or epidermal encrustation in the majority of animals, the changes being severe at 100 and 200 mg/kg/day. Treatment with teicoplanin was associated with a decrease of body weight gain (18%) and of food consumption (20%) at the highest dose of 200 mg/kg. Gross examination of animals sacrificed on the 21st day of gestation revealed a dose-related inflammation at the injection site, and pale kidneys in a few (5%) females treated with 50 and 100 mg/kg teicoplanin, and in approximately 30% of the animals treated with 200 mg/kg.

Fertility and gestation indices, length of gestation and pre-implantation loss were comparable in all groups; there were no modifications as a result of treatment with teicoplanin.

Litter data of females sacrificed on day 21 of gestation, as assessed by litter size, pre-and post-implantation loss and resorption rate, incidence of live fetuses, litter and mean fetus weight, incidence of fetal malformations and minor anomalies, did not appear to be affected by treatment at any dose.

Analysis of the litter data from females allowed to deliver showed a significant increase of stillborn pups at 100 and 200 mg/kg and of mortality among sucklings during the first 4 days post-partum at 200 mg/kg (see table below).

	Control	LD	MD	HD
Pups alive at birth	47	89	82	59
Stillborn	0	0	9	15
Gestation survival index	100	100	90	80
Pups alive at day 4	46	88	78	51
Pups dead days 0-4	1	1	4	8
Viability index	98	99	95	86
Pups alive on day 21 (weaning)	46	88	78	51
Pups dead days 5-21	0	0	0	0
Lactation index	100	100	100	100

Other litter data, such as weight at birth, body weight gain of offspring, and lactation index, were not adversely affected by treatment at any dose. No drug-related gross changes were found at necropsy of pups (sacrificed after weaning).

It was suggested that the reduction in the gestation survival and viability indices at 200 mg/kg teicoplanin was in response to reduced maternal care, which was due to severe inflammation at the injection site causing excessive stress. There was no apparent teratogenic activity associated with the administration of teicoplanin at any dose. Maternal toxicity was evident at the 200 mg/kg dose.

ND **9.1.3 Reproductive toxicity and peri- and post-natal development SC study. Report No. 1109. Report date 02/02/1984. Toxicology department, Gerenzano. QA/GLP yes.**

A comprehensive reproductive toxicity and peri- and post-natal development study was conducted in CD Sprague-Dawley rats using the lyophilised sodium salt of teicoplanin dissolved in distilled water. Doses were 10, 20 and 40 mg/kg and were administered by the SC route. Controls received 0.9% saline.

F_0 male fertility (modified dominant lethal study).

Male rats (20/group) received teicoplanin from 10 weeks prior to pairing on a 1:2 basis with untreated females. Treatment continued for 2 weeks after pairing. Males were killed either at the end of the breeding period (10/group) or after the females were killed. Females were killed on day 21 of gestation, and uteri and fetuses were examined after cesarean section.

Clinical signs were mainly development of lesions at the site of injection. Skin thickening, alopecia and epidermal encrustations with slight or moderate focal subcutaneous ecchymosis developed in some MD males by week 4, and in all HD males by week 2 of treatment, and persisted thereafter. The lesions were most severe in the HD group, where they were associated with fibrotic subcutaneous tissue or abscesses and local muscle necrosis. The general condition of HD rats was also reported to be fair compared with other rats. No other clinical signs were reported.

One HD male died during treatment and was found to have an increased splenic volume on autopsy. This was not considered to be related to treatment, but increased splenic volume was also found in 1 MD and 5 other HD rats killed at the end of treatment. Fibrotic adhesions of the spleen with peritoneum were also found in 4 HD males. There were no other notable findings in F_0 males at autopsy, including no effects on testes weight.

Body weight was reduced by 4-17% from 5 weeks until the end of treatment in the HD group, and by 2-7% in the MD group during the last 2 weeks of treatment. Food consumption was reduced by 10-15% in the HD group only.

Treatment of males with teicoplanin had no effect on the following parameters: pre-coital interval, the number of females becoming pregnant, mean number of live fetuses, mean litter and fetal weights, and fetal sex ratio. There were also no differences in the number of fetuses with minor anomalies and major malformations (assessed mainly by external examination only).

The number of post-implantation losses, resorptions and corpora lutea were slightly, but not significantly, reduced in treatment groups (not related to dose). A significant increase in the number of pre-implantation losses was recorded in all treatment groups (8-9.4) compared with controls (3.2), but this was said to be within the range of findings in historical controls (5.7-28.9, mean of 13.5). It was concluded that teicoplanin probably does not have dominant lethal mutagenic effects since post-implantation losses and fetal parameters were not affected.

F_0 female fertility.

Female rats (24/group) received teicoplanin from 15 days prior to pairing with untreated males until up to 21 days post-partum. Females were killed either on day 21 of gestation (12/group; and uteri and fetuses were examined after cesarean section) or 21 days after being allowed to litter.

Skin lesions similar to those found in treated males (see above) were also seen in a few LD rats and all MD and HD rats. No other clinical signs were reported, and there were no effects on food consumption or body weight throughout treatment, and no mortalities.

Treatment with teicoplanin had no statistically significant effects on the following parameters: oestrous cycles, pre-coital interval, the number of females becoming pregnant, the number of females with full term pregnancies, the duration of pregnancy, the number of resorptions, the number of corpora lutea, pre- and post-implantation losses, total number of live fetuses (females killed at day 21) and fetal weight (females killed at day 21). There were no differences in the number of fetuses with minor anomalies and major malformations, and no treatment related abnormalities were found in still-born fetuses or pups dying during the lactation period.

Treatment with teicoplanin was reportedly not associated with difficulties during parturition. The total number of pups (live + stillborn) delivered to HD dams was significantly reduced (124 compared with 151 for controls), and 5% of these in the HD group were still-born (compared with 0 controls, but not statistically significant). There were no differences in litter viability to day 21 (lactation index). A slight increase in the number of male pups, and a corresponding decrease in the number of female pups was also found at the HD, but the significance of this is not clear. Total litter weight was reduced by about 3-10% in all treated groups over 21 days (occasionally statistically significant, but not dose related).

F_1 development.

Treatment with teicoplanin had no effect on physical, motor, neurological and behavioural development of pups up to day 30-41, as assessed by a wide range of developmental tests.

F_1 reproduction.

Offspring from treated F_0 females from the female fertility study were used to assess the reproductive function of untreated F_1 rats (2/sex/litter; 20-24/sex/group). Investigations were similar to those conducted for the F_0 female fertility study (except determination of oestrous cycles), with F_1 females killed either at 21 days of gestation or 21 days post-partum.

No clinical signs or mortalities related to treatment were reported. There were also no significant differences in the body weight or food consumption of F_1 rats throughout pre-breeding, gestation and lactation periods.

Treatment of F_0 rats with teicoplanin had no effect on F_1 male and female reproduction parameters, fetal and pup parameters, and F_2 pup development up to 26-41 days of age. No differences in the incidence of minor anomalies or major malformations were found in fetuses from dams killed at day 21 of gestation or still-born, or in pups dying during the lactation period.

Peri-natal and post-natal study.

Pregnant rats (20/group) were treated with teicoplanin from day 15 of gestation to day 21 post-partum. Dams were killed 21 days post-partum.

Clinical signs consisted of skin lesions (as described above) at the site of injection in 1 LD, some MD and most HD rats. There were no treatment-related mortalities, and no effects on body weight or food consumption throughout the study.

Treatment with teicoplanin had no significant effect on the duration of pregnancy, number of dams littering and weaning, number of live pups/dam up to 21 days post-partum, and pup sex ratios. The number of pups delivered by HD dams was lower compared with controls (151 compared with 191 for controls), but litter viability to day 21 and lactation indices were unaffected. Mean pup weight for all treated groups showed a significant 5-11% reduction compared with controls, and this persisted for at least 21 days.

There were no differences in the incidence of minor anomalies or major malformations in still-born fetuses or pups dying during the lactation period, and no treatment related abnormalities were found in weaned pups sacrificed at 21 days.

9.2 Rabbit

9.2.1 Preliminary fetal toxicity SC study (G. Lepetit, Sept 1982).

A dose-range finding study was carried out in pregnant female New Zealand white rabbits by administering teicoplanin SC at doses of 0, 1, 2.5, 5, 10, 15, 25, 50, 100 and 150 mg/kg/day from day 6-18 of pregnancy. Most groups consisted of 4 does, but the control and the 5 and 10 mg/kg groups had 8 does each.

During the study a number of deaths occurred in the following groups:

	Dose of teicoplanin (mg/kg)				
	0	**25**	**50**	**100**	**150**
Mortality	1/8	2/4	3/4	3/4	3/4

Most deaths were recorded during the last third of pregnancy, after the cessation of treatment. In the control female, the 2 females at 25 mg/kg and in one of each of the 50 and 100 mg/kg groups, death was proceeded by interruption of pregnancy (abortion).

Pregnancy was affected at doses of 25 mg/kg or higher, with abortion occurring in all remaining females of these groups (one exception at 25 mg/kg). There was no evidence of a teratogenic effect as a result of the administration of teicoplanin in the rabbit.

Following this study, a dose level of approximately 15 mg/kg was to be used for the extended teratogenicity study.

9.2.2 Fetal toxicity and teratogenicity IM study (G. Lepetit, Aug 1983).

Teicoplanin was administered IM to pregnant NZ white rabbits (15/group) on days 6-18 of gestation at doses of 0, 2.5, 5, 10, and 15 mg/kg/day per groups. Does were sacrificed on day 29 of gestation and their uterine contents examined.

No maternal deaths occurred and all pregnant animals carried their litter to term or the sacrifice date (no abortions). Over the course of the study there were no observable clinical signs. Bodyweight gain was not linear for any group (including controls) over the duration of the study. Groups receiving 2.5 and 5.0 mg/kg had a slightly greater bodyweight gain than control over the duration of the study, while the higher dose groups (10 and 15 mg/kg) had a reduced bodyweight gain (lower than control) up until the last week of the study. During the last week, the bodyweight gain of both high dose groups exceeded the control gain.

Pregnancy rate was unaffected by treatment and no interruptions of pregnancy (abortions) occurred. Treatment with teicoplanin (any dose) had no affect on pre-implantation loss and the number of corpora lutea. At all dose levels, litter sizes were slightly lower (10%) than that of controls, but differences were not statistically significant and were unrelated to the dose used. The resorption rate and post-implantation loss for all treatment groups were comparable to the control group. Concurrent with the slight decrease of litter size was a slight, non-significant reduction in litter weights; fetal bodyweights were not adversely affected by teicoplanin treatment.

Arhinia was found in two control fetuses and in 1 fetus of the 5 mg/kg group. No malformed fetuses were found at the 2.5, 10 and 15 mg/kg dose levels. No minor anomalies were recorded at the external examination, but minor visceral and skeletal anomalies were observed in some fetuses of all groups including the control group. The highest frequencies were observed in the 5, 10 and 15 mg/kg groups, but the values were inversely proportional to the doses used.

Teicoplanin at the doses used, did not appear to display either embryo- or fetotoxic effects, and it lacked teratogenic activity.

Table 1: MIC Values

Organisms (No. Tested)	Antimicrobial Agents	MIC Range (mcg/ml)	MIC for % of isolates 50	90
Staphylococcus aureus (20)	teicoplanin	0.2 - 1.6	0.4	0.4
	vancomycin	0.4 1.6	0.8	1.6
	ampicillin	0.025 - 6.3	0.4	6.3
	cephaloridine	0.013 - 3.1	0.1	0.4
	erythromycin	0.05 - > 100	0.4	> 100
	lincomycin	0.2 - > 100	0.8	12.5
Staphylococcus epidermidis (20)	teicoplanin	0.05 - 3.1	0.8	1.6
	vancomycin	0.2 - 3.1	1.6	3.1
	ampicillin	0.013 - 6.3	0.4	3.1
	cephaloridine	0.025 - 0.2	0.05	0.2
	erythromycin	0.05 - > 100	0.4	> 100
	lincomycin	0.4 - > 100	0.4	> 100
Streptococcus pyogenes (19)	teicoplanin	0.025 - 0.1	0.05	0.1
	vancomycin	0.8 - 0.8	0.8	0.8
	ampicillin	0.006 - 0.05	0.013	0.025
	cephaloridine	0.006 - 0.1	0.013	0.02
	erythromycin	0.013 - 0.2	0.05	0.2
	lincomycin	0.006 - 0.1	0.05	0.1
Streptococcus pneumoniae (19)	teicoplanin	0.05 - 0.1	0.1	0.1
	vancomycin	0.2 - 0.8	0.8	0.8
	ampicillin	0.013 - 1.6	0.025	0.8
	cephaloridine	0.013 - 0.8	0.05	0.4
	erythromycin	0.01 - 0.2	0.025	0.1
	lincomycin	0.05 - 0.4	0.2	0.4
Streptococcus faecalis (20)*	teicoplanin	0.2 - 0.4	0.4	0.4
	vancomycin	0.8 - 3.1	1.6	1.6
	ampicillin	0.9 - 1.6	1.6	1.6
	cephaloridine	3.1 - 25	25	25
	erythromycin	0.4 - > 100	3.1	100
	lincomycin	0.4 - > 100	25	> 100
Other streptococci (12)**	teicoplanin	0.025 - 0.2	0.1	0.2
	vancomycin	0.8 - 1.6	0.8	1.6
	ampicillin	0.025 - 0.2	0.05	0.1
	cephaloridine	0.006 - 0.4	0.025	0.2
	erythromycin	0.006 - 0.3	0.025	0.4
	lincomycin	0.025 - >12.5	0.1	0.8

*Includes 2 *Str. faecium* strains

***Str. agalaciae* (4); *Str. bovis* (1); *Str. mitis* (2); *Str. mutans* (2); *Str. salivarius* (1); *Str. sanguis* (1); *Streptococcus* sp. (1)

1.1.2 Activity against Gram-positive bacilli (Ref. 3, 4, 11, 13, 15, 16)

The *in vitro* activity against gram-positive anaerobic bacilli was studied in bacteria cultures grown on Wilkins-Chalgren agar. The results shown on Table 2 show that teicoplanin is relatively more potent than vancomycin for *Clostridium* and *Propionibacterium*. The activity against *Listeria monocytogenes* and gram-positive aerobic diptheroids (Group J/k) was comparable to those of vancomycin.

Table 2: Activity Against Gram-Positive Rods

Organisms	No. Tested	MIC (mcg/mL) Teicoplanin	Vancomycin	References
Clostridium perfringens	10	0.117	0.175	15
	1	0.10	1.60	3,4
	3	3.20	6.40	13
Clostridium difficile	10	0.125	0.50	15
	3	0.40	1.60	3,4
	5	0.80	3.20	13
Clostridium septicum	5	0.25	0.40	15
Propionibacterium acnes	12	0.40	0.80	3,4
	3	1.60	1.60	13
Listeria monocytogenes	26	0.80	1.60	11
Group J/K diphtheroids	8	0.80	0.80	16
	7	1.60	0.80	11

Ref:

3	B2.2 p93
4	B2.2 p100
11	B2.2 p143
13	B2.2 p149
15	B2.2 p158
16	B2.2 p161

1.1.3 Activity against some multiresistant clinical strains (Ref. 3).

The following MIC values show the activity of teicoplanin on methicillin resistant strains of staph. aureus and other multiresistant clinical isolates of staph. epidermidis, str. pneumoniae and str. faecalis. All of these strains were sensitive to both teicoplanin and vancomycin.

Table 3: The activity of teicoplanin on multiresistant clinical strains.

Strains		Resistances	Teicoplanin MIC mcg/mL
Staph. aureus	L1096	pe,me,te,er,km,sm	0.4
	L1097	pe,me,te,er,ln,to,km,sm,rf	0.4
	L1098	pe,me,te,er,ge,km,sm	0.4
	L1398	pe,te,er,km,sm	0.4
	L1400	pe,te,er,ge,to,km,sm,ln	0.4
Staph. epidermidis	L835	pe,me,te,cm,er,ln,rf	0.4
	L836	pe,me,te,cm,rf	0.8
	L843	pe,rf	1.6
	L874	pe,rf	1.6
	L748	pe	0.8
	L862	pe	0.4
	L790	pe	1.6
Str. pneumoniae	L1174	pe,cm	0.1
	L1190	pe	0.1
	L1192	pe	0.1
	L1191	pe,te,sxt	0.1
	L1193	pe,te,cm	0.1
	L1194	pe,te,cm,ln,er,sxt	0.1
Str. faecalis	L839	cxm,rf	0.4

pe: penicillin G; me: methicillin; te: tetracycline; cm: chloramphenicol; er: erythromycin; ln: lincomycin; to: tobramycin; ge: gentamicin; km: kanamycin; sm: streptomycin; sxt: co-trimoxazole; cxm: cefuroxime; rf: rifampicin.

Ref:
3 B2.2 p93

PRODUCT INFORMATION

TARGOCID
(TEICOPLANIN)

Composition: Teicoplanin

Actions: Anti-microbial

Microbiology:

Teicoplanin is generally bactericidal on growing populations of Gram-positive organisms; bactericidal synergism has been demonstrated with aminoglycosides.

One-step resistance to teicoplanin has not been obtained *in vitro*.

Teicoplanin has shown no cross-resistance to beta lactam antibiotics, macrolides, aminoglycosides, tetracycline, rifampicin or chloramphenicol.

Pharmacokinetics:

Following injection, teicoplanin rapidly penetrates into tissues, including skin, fat and bone -and reaches the highest concentrations in the kidney, trachea, lungs and adrenals. Teicoplanin does not readily penetrate into the cerebro-spinal fluid (CSF).

In man, the plasma level profile after intravenous administration indicates a biphasic distribution (with a rapid distribution phase having a half-life of about 0.3 hours, followed by a more prolonged distribution phase having a half-life of 3 hours), followed by a slow elimination (with an elimination half-life of 70-100 hours). The apparent volume of distribution at steady state is similar to total body water, i.e. 0.6 L/kg. The volume of distribution in children is not substantially different from that in adults.

Approximately 90-95% teicoplanin is bound with weak affinity to plasma proteins. Teicoplanin penetrates readily into blister exudates and into joint fluid; it penetrates neutrophils and enhances their bactericidal activity; it does not penetrate red blood cells.

No metabolites of teicoplanin have been identified; more than 97% of the administered teicoplanin is excreted unchanged.

The elimination of teicoplanin from plasma is prolonged with a terminal half-life of elimination in man of 70-100 hours. Teicoplanin is excreted mainly in urine.

Indications:

Targocid is indicated in the treatment of Gram-positive bacterial infections, even in those patients with organisms resistant to standard therapy (including methicillin and cephalosporins) or who are allergic to penicillins and cephalosporins. Such infections include endocarditis, septicaemia and osteomyelitis, respiratory infections, skin and soft tissue infections, urinary tract infections and peritonitis associated with chronic ambulatory peritoneal dialysis (CAPD).

Targocid is also recommended for prophylaxis in those patients in whom infection with Gram-positive organisms would constitute a hazard (for example in patients requiring cardiac, dental or orthopaedic surgery).

Contra-indications:

Targocid is contra-indicated in patients with known hypersensitivity to the drug.

Warnings and Precautions:

Periodic haematological studies, and renal and liver function tests are advised during prolonged treatment. Serial renal and auditory function tests should be undertaken in the following circumstances:

- Prolonged treatment in patients with renal insufficiency.
- Concurrent and sequential use of other drugs which may have neurotoxic properties. These include aminoglycosides, amphotericin, cyclosporin, cysplatin, frusemide and ethacrynic acid.

However, there is no evidence of synergistic toxicity with these combinations and Targocid.

Targocid should be administered with caution in patients known to be hypersensitive to vancomycin since cross-sensitivity may occur. However, a history of the "Red Man Syndrome" that can occur with vancomycin is not a contra-indication with Targocid.

Interactions:

In clinical trials Targocid has been administered to many patients already receiving various medications including other antibiotics, antihypertensives, cardiac drugs, and antidiabetic agents, without evidence of adverse interaction.

Use in Pregnancy and Lactation:

Although animal reproduction studies have not shown impairment of fertility, teratogenic, embryotoxic or fetotoxic effects, Targocid should not be used during confirmed or presumed pregnancy or during lactation unless the potential benefits outweigh possible risks.

Adverse Reactions:

Targocid is generally well tolerated. The following adverse effects have been reported:

- Local reactions: pain, phlebitis, redness, abscess
- Hypersensitivity: skin rash, erythema or pruritus, fever, bronchospasm or anaphylaxis
- Hepatic: transient abnormality of transaminases and/or alkaline phosphatase
- Haematologic: eosinophilia, thrombocytopenia, leucopenia
- Renal: transient rise in serum creatinine
- Gastrointestinal: nausea or vomiting, diarrhoea
- Nervous system: dizziness, headache
- Auditory: Mild hearing loss, tinnitus or vestibular disorder

Overdosage:

Treatment of overdosage should be symptomatic. Teicoplanin is not removed by haemodialysis or peritoneal dialysis.

Dosage and administration:

The reconstituted Targocid injection should be administered directly either intravenously or intramuscularly. Intravenous dosing may be rapid over one minute, or more slowly by infusion. Dosage is usually once daily but a second dose may be given on the first day, for rapid attainment of high plasma levels in cases of severe infection.

Adults: On the first day, Targocid should be administered at a dose of 400mg (approximately 6mg/kg); on subsequent days the dose should be 400mg or 200 mg (approximately 3mg/kg). The higher dose and intravenous route are recommended in severe infections. In life-threatening conditions two 6mg/kg doses should be given at intervals of 12 hours on the first day, followed by 6mg/kg daily on subsequent days.

Elderly Patients: As for adults. If renal function is severely impaired, the instructions for impaired renal function should be followed.

Children: In patients under 14 years, doses of 6mg/kg should be given every 12 hours, or the first three doses, followed by 3mg/kg daily. This will provide adequate coverage for most infections caused by susceptible organisms. In severe infections a daily dose of 6mg/kg is recommended. Doses of up to 12mg/kg daily are recommended in granulocytopenic patients.

When serum concentrations of teicoplanin are monitored in severe infections, trough levels (immediately before the subsequent dose) should be in the range of 5-15mg/L.

The majority of patients with infections caused by organisms sensitive to teicoplanin show a therapeutic response within 48-72 hours. The total duration of therapy is determined by the type and severity of the infection, and the clinical response of the patient. In endocarditis and osteomyelitis, treatment for three weeks or longer is recommended.

Patients with Renal Impairment:

Patients with acute or chronic renal impairment should be administered the normal recommended dose for the first few days. As with other antibiotics of this type, in renal insufficiency it is better to vary the dosing interval rather than the dose to maintain seum trough levels in the range 5-15mg/L. Adequate serum levels are usually maintained in cases of mild to moderate renal insufficiency (creatinine clearance 10-80 ml/min), with a dose of 200mg to 400mg daily or every two days; and in cases of severe renal insufficiency (creatinine clearance less than 10ml/min), with a dose of 200mg every 2-3 days.

Targocid has been used to treat peritonitis in patients undergoing chronic ambulatory peritoneal dialysis (CAPD). The usual dose has been 50mg in each two litre bag of dialysis fluid for the first 48 hours, and 25mg in each two litre bag thereafter. Egress from the peritoneal fluid is slow.

Prophylaxis:

Adults: For Gram-positive cover during and after surgery (for example dental, orthopaedic or cardiovascular operations), an intravenous injection of 400mg Targocid should be given at the time of induction of anaesthesia. In cardiac surgery a further dose of 400mg should be given at the end of surgery, and another 400mg dose 24 hours later.

Preparation of Injection:

The entire contents of the water ampoule should be slowly added to the vial of Targocid and the vial rolled gently until the powder is completely dissolved, taking care to avoid foam formation. If the solution does become foamy, allow to stand for 15 minutes for the foam to subside. Satisfactory potency of the reconstituted injection is retained for 48 hours at room temperature and for 7 days at 4°C.

The reconstituted solution may be injected directly, or alternatively diluted with:

- 0.9% Sodium Chloride solution
- Compound sodium lactate solution

If necessary, these solutions may be stored at 4°C for up to 7 days. Solutions left at room temperature for longer than 24 hours should be discarded.

- 5% Dextrose solution
- 0.18% Sodium Chloride and 4% Dextrose solution

These solutions should be used within 24 hours; solutions kept longer than 24 hours should be discarded.

- Peritoneal dialysis solutions containing 1.36% or 3.86% dextrose. Such solutions are chemically stable for up to 28 days at 4°C. Teicoplanin is also stable in peritoneal solutions containing insulin or heparin at body temperature (37°C) for 48 hours.

Presentation

- Targocid 100mg- 5ml vial containing lyophilised 125mg* teicoplanin and 14mg sodium chloride with an accompanying ampoule Water for Injections (Ph. Eur.)

- Targocid 200mg- 10ml vial containing lyophilised 220mg* teicoplanin and 24mg sodium chloride with an accompanying ampoule Water for Injections (Ph. Eur.)

- Targocid 400mg- 20ml vial containing lyophilised 460mg* teicoplanin and 24mg sodium chloride with an accompanying ampoule Water for Injections (Ph. Eur.)

* An overage is included to allow withdrawal of the correct dose.

Further information available from Merrell Dow Pharmaceuticals
26 Rodborough Rd
Frenchs Forest
NSW 2086

THERAPEUTIC GOODS ADMINISTRATION - AUSTRALIA
PRECLINICAL EVALUATION OF REGISTRATION APPLICATION

APPLICANT:	Marion Merrell Dow Ltd
DRUG NAME:	Teicoplanin
TRADE NAME:	Targocid
DOSE STRENGTH/FORM:	100, 200 and 400 mg powder for injection
EVALUATOR:	XXXXXXXXXXXXXXXXX
APPLICATION NO:	91-156-2
FILE NOs:	91/10911; 93/11783

This evaluation has been checked for confidential material and is cleared for release to the sponsor provided that pages 1, 17 and 53 are substituted with the attached pages.

SUMMARY:

1. Marion Merrell Dow Ltd have applied to register the glycopeptide antibiotic teicoplanin for IM and IV use in the treatment of a number of infections involving gram-positive bacteria (for example, endocarditis, septicaemia, osteomyelitis, peritonitis and infections of the urinary tract and soft tissues), and in surgical patients. The proposed dosage is 400 mg (about 6 mg/kg) on day 1, and 200 mg/kg/day (about 3 mg/kg/day) or 400 mg/day thereafter, possibly for up to 3 weeks.

   A detailed preclinical evaluation for teicoplanin was prepared by XXXXXXXXXXXXX in 1986 for a clinical trial application (approved in May 1987). For the current application, the sponsor has submitted a further reproductive toxicity study, and evaluation of this is incorporated into the previous clinical trial evaluation.

2. Teicoplanin is chemically related to the vancomycin-ristocetin group of antibiotics. It has both bactericidal and bacteriostatic activity, with the bacteriostatic mechanism of action being similar to that of vancomycin.

   Teicoplanin is active *in vitro* against aerobic and anaerobic gram-positive bacteria, including methicillin-resistant Staphylococci, Group D Streptococci, Clostridium difficile and group JK corynebacteria. Very weak or no activity was shown against gram-negative bacteria.

   The *in vitro* activity of teicoplanin was supported by studies *in vivo* in mice (SC) and rabbits (IV), where teicoplanin was effective against infections due to susceptible organisms. In addition, teicoplanin combined with gentamicin was 2.5 times more effective than teicoplanin alone in the treatment of endocarditis in rabbits.

3. In the anaesthetised dog, an IV dose of 10 mg/kg teicoplanin resulted in slight but significant decreases in blood pressure, cardiac output and stroke volume. These changes were not observed in the conscious dog. Teicoplanin at doses > 3 mg/kg in mice and rats produced behavioural changes and, at 300 and 600 mg/kg, signs of CNS depression. Teicoplanin, at concentrations up to 5000 μg/mL *in vitro*, did not interfere with platelet function.

after 1 month of treatment (lower margins after 6 months treatment), but < 1 to 2.4 times greater in rats after 1 or 6 months of treatment. Thus, the safety margin for the development of renal toxicity was good according to the data in dogs, but poor according to the data in rats. However, it should be noted that because of the poor pharmacokinetic data (including lack of metabolic studies), the suitability of either species as a model for humans is uncertain. The renal toxic effects in all of the dog studies and in the 6 month rat study were reversible over 9-10 weeks after treatment had ceased.

The nephrotoxicity of teicoplanin, on a dose for dose basis, was found to be comparable to that of vancomycin in an 8 day SC study in rats. However, this study was of limited use because of the absence of pharmacokinetic data for vancomycin.

In conclusion, there were considerable deficiencies in the preclinical data. The kidneys were identified as the target organs for toxicity, and there was evidence to suggest that the effect may be clinically relevant. However, teicoplanin has similar properties to vancomycin, and may, in some cases, be of some clinical advantage. Therefore, from a preclinical point of view, there are no objections to the registration of teicoplanin provided that its use is restricted to cases where vancomycin would normally be used. Preclinical approval is also based on assumptions that the clinical evaluator has assessed the issues associated with possible adverse renal effects, and that this is reflected in the product information.

XXXXXXXXXXXXXXXX
Drug Toxicology
Evaluation Section

23-Sep-1993

injection of ethacrynic acid. Controls (3/group) received teicoplanin followed by saline. The maximum output of the AC cochlear potential was similar in all groups of animals, and did not differ from values obtained in other experiments using untreated controls. However, although the cochlear hair cell count was similar to that found in previous controls (about 3%) at the LD and MD of teicoplanin (with or without ethacrynic acid), at the 400 mg/kg dose (plus saline, teicoplanin was associated with a 10% loss in hair cells. The significance of this latter finding is unclear, but the results with teicoplanin 400 mg/kg plus ethacrynic acid were not given.

It should be noted that the ototoxic effects of XXXXXXXXXXX (≥ 93 mg/kg IP for 7 days) were detected in the preyer pinna reflex test and in tests of the ability of the cochlear to generate potentials in response to sounds in cats.

7 CARCINOGENICITY - No data presented

8 GENOTOXICITY

8.1 Histidine reversion in Salmonella typhimurium

Three separate studies were carried out to investigate the mutagenic activity of teicoplanin in the histidine reversion test in Salmonella typhimurium. Because Salmonella typhimurium (strains TA 98, 100, 1535, 1537 and 1538) is a gram-negative organism, teicoplanin can be effectively assessed by this system. All studies used positive controls, which were effective, and were carried out in the presence and absence of metabolic activation (± S9). The strains TA 100 and TA98 carried plasmids. In the first study, a dose range of 1 to 1000 μg/plate teicoplanin resulted in a 50% plating efficiency at the highest dose (1000 μg/plate), and no mutagenic effect. In the other studies, a dose range of 30 to 5000 μg/plate resulted in a 13% plating efficiency at the highest dose (5000 μg/plate), and no mutagenic activity.

8.2 Gene conversion test in Saccharomyces cerevisiae D4.

Two colony types of Saccharomyces cerevisiae D4 were used in this study, the tryptophan^{+} and the adenine^{+}. The tests were carried out using positive controls and in the presence and absence of metabolic activation (± S9). A dose range of 500 to 4000 μg/mL teicoplanin was used with no dramatic toxic affect on the culture (67% survival) and no mutagenic activity.

8.3 Point mutation test in Schizosaccharomyces pombe.

The yeast strain Schizosaccharomyces pombe was used to test for forward point mutation induced by teicoplanin. A positive control was used and the test was carried out in the presence and absence of metabolic activation. A concentration range of 250 to 2000 μg/mL teicoplanin was used in this study. The survival rate of the test cells was never less than 82% (+ S9), the positive control was effective (20 times increase above negative controls), and teicoplanin did not induce an increased in mutation above the level seen for the negative control.