TICOCIN Injection (Teicoplanin)

**Composition**

TICOCIN-200
Each vial contains:
Teicoplanin IP..................................... 200 mg
As sterile freeze-dried powder for reconstitution with 3 ml Sterile Water for Injections IP
Each 3 ml of reconstituted injection contains
Teicoplanin IP......200 mg

TICOCIN-400
Each vial contains
Teicoplanin IP..................................... 400 mg
As sterile freeze-dried powder for reconstitution with 3 ml Sterile Water for Injections IP
Each 3 ml of reconstituted injection contains
Teicoplanin IP......200 mg

**Dosage Form**

Sterile freeze dried powder for reconstitution for intravenous (IV) / intramuscular (IM) use only.

**Pharmacology**

*Pharmacodynamics*

Teicoplanin is a bactericidal, glycopeptide antibiotic.

*Mode of Action*

Teicoplanin inhibits the growth of susceptible organisms by interfering with cell wall biosynthesis at a site different from that affected by beta-lactams. Peptidoglycan synthesis is blocked by specific binding to D-alanyl-D-alanine residues.

*Mechanism of Resistance*

Resistance to teicoplanin can be based on the following mechanisms:

The modified target structure form of resistance has occurred particularly in *Enterococcus faecium*. The modification is based on exchange of the terminal D-alanine-D-alanine function of the amino acid chain in a murein precursor with D-Ala-D-lactate, thus reducing the affinity to vancomycin. The responsible enzymes are a newly synthesised D-lactate dehydrogenase or ligase.

The reduced sensitivity or resistance of staphylococci to teicoplanin is based on the overproduction of murein precursors to which teicoplanin is bound.

Cross-resistance between teicoplanin and the glycoprotein, vancomycin, may occur. A number of
vancomycin-resistant enterococci are sensitive to teicoplanin (Van-B phenotype).

Susceptibility
The prevalence of resistance may vary geographically and over time for selected species and local information on resistance is desirable, particularly when treating severe infections. Where necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species

Aerobic Gram-positive bacteria
Corynebacterium jeikeium
Enterococcus faecalis
Staphylococcus aureus (including methicillin-resistant strains)
Streptococcus agalactiae
Streptococcus dysgalactiae subsp. equisimilis
(Group C and G streptococci)
Streptococcus pneumoniae
Streptococcus pyogenes
Streptococci in the viridans group

Anaerobic Gram-positive bacteria
Clostridium difficile
Peptostreptococcus spp.

Species for which acquired resistance may be a problem

Aerobic Gram-positive bacteria
Enterococcus faecium
Staphylococcus epidermidis
Staphylococcus haemolyticus
Staphylococcus hominis

Inherently resistant bacteria
All Gram-negative bacteria

Other bacteria
Chlamydia spp.
Chlamydophila spp.
Legionella pneumophila
Mycoplasma spp.

Pharmacokinetics

Teicoplanin exhibited linear pharmacokinetics at a dose range of 2 to 25 mg/kg.

Absorption
Teicoplanin is administered by the parenteral route (intravenously or intramuscularly). After IM administration, the bioavailability of teicoplanin (as compared to IV administration) is almost complete (90%). After six daily IM administrations of 200 mg, the mean (SD) maximum teicoplanin concentration (C_{max}) amounted to 12.1 (0.9) mg/L and occurred at 2 hours after administration.
After a loading dose of 6 mg/kg administered intravenously every 12 hours for 3 to 5 administrations, \( C_{\text{max}} \) values range from 60 to 70 mg/L and \( C_{\text{trough}} \) are usually above 10 mg/L. After an intravenous loading dose of 12 mg/kg administered every 12 hours for 3 administrations, mean values of \( C_{\text{max}} \) and \( C_{\text{trough}} \) are estimated to be around 100 mg/L and 20 mg/L, respectively.

After a maintenance dose of 6 mg/kg administered once daily \( C_{\text{max}} \) and \( C_{\text{trough}} \) values are approximately 70 mg/L and 15 mg/L, respectively. After a maintenance dose of 12 mg/kg once daily \( C_{\text{trough}} \) values range from 18 to 30 mg/L.

**Distribution**

The binding to human serum proteins ranges from 87.6 to 90.8%, without any variation in function of the teicoplanin concentrations. Teicoplanin is mainly bound to human serum albumin. Teicoplanin is not distributed into red cells.

The volume of distribution at steady state (Vss) varies from 0.7 to 1.4 mL/kg. The highest values of Vss were observed in the recent studies where the sampling period was more than 8 days.

Teicoplanin is distributed mainly in lung, myocardium and bone tissues with tissue/serum ratios superior to 1. In blister fluids, synovial fluid and peritoneal fluid, the tissue/serum ratios ranged from 0.5 to 1.

Elimination of teicoplanin from peritoneal fluid occurs at the same rate as from serum. In pleural fluid and subcutaneous fat tissue, the tissue/serum ratios are between 0.2 and 0.5. Teicoplanin does not readily penetrate into the cerebrospinal fluid (CSF).

**Metabolism**

Unchanged form of teicoplanin is the main compound identified in plasma and urine, indicating minimal metabolism. Two metabolites are formed, probably by hydroxylation, and represents 2 to 3% of the administered dose.

**Elimination**

Unchanged teicoplanin is mainly excreted by the urinary route (80% within 16 days) while 2.7% of the administered dose is recovered in the faeces (via bile excretion) within 8 days following administration.

Elimination half-life of teicoplanin varied from 100 to 170 hours in the most recent studies where blood sampling duration was about 8 to 35 days.

Teicoplanin has a low total clearance in the range of 10 to 14 mL/h/kg and a renal clearance in the range of 8 to 12 mL/h/kg, indicating that teicoplanin is mainly excreted by renal mechanisms.

**Special Populations**

**Renal Impairment**

As teicoplanin is eliminated by the renal route, teicoplanin elimination decreases according to the degree of renal impairment. The total and renal clearances of teicoplanin depends on the creatinine clearance.

**Geriatric**

In the elderly population, the teicoplanin pharmacokinetics is not modified unless in case of renal impairment.

**Paediatric**

A higher total clearance (15.8 mL/h/kg for neonates, 14.8 mL/h/kg for a mean age 8 years) and a shorter elimination half-life (40 hours neonates; 58 hours for 8 years) are observed compared to adult patients.

**Pharmacokinetic/Pharmacodynamic Relationship**

Teicoplanin antimicrobial activity depends essentially on the duration of time during which the substance level is higher than the minimum inhibitory concentration (MIC) of the pathogen.

**Indications**
TICOCIN is indicated for use in serious Gram positive infections, staphylococcal infections in patients sensitive or unresponsive to penicillin and cephalosporins, continuous ambulatory peritoneal dialysis (CAPD) related peritonitis, prophylaxis in orthopaedic surgery at risk of Gram positive infections.

**Dosage And Administration**

**Dosage**
The dose and duration of treatment should be adjusted according to the underlying type and severity of infection and clinical response of the patient, and patient factors such as age and renal function.

**Measurement of Serum Concentrations**
Teicoplanin trough serum concentrations should be monitored at steady state after completion of the loading dose regimen in order to ensure that a minimum trough serum concentration has been reached:
For most Gram-positive infections, teicoplanin trough levels of at least 10 mg/L when measured by High Performance Liquid Chromatography (HPLC), or at least 15 mg/L when measured by Fluorescence Polarization Immunoassay (FPIA) method.
For endocarditis and other severe infections, teicoplanin trough levels of 15-30 mg/L when measured by HPLC, or 30-40 mg/L when measured by FPIA method.
During maintenance treatment, teicoplanin trough serum concentrations monitoring may be performed at least once a week to ensure that these concentrations are stable.

**Adults and Elderly Patients with Normal Renal Function**

<table>
<thead>
<tr>
<th>Indications</th>
<th>Loading dose regimen</th>
<th>Targeted trough concentrations at day 3 to 5</th>
<th>Maintenance dose</th>
<th>Targeted trough concentrations during maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Complicated skin and soft tissue infections</td>
<td>400 mg IV or IM</td>
<td>$&gt;15 \text{mg/L}^1$</td>
<td>6 mg/kg body weight IV or IM once a day</td>
<td>$&gt;15 \text{mg/L}^1$ once a week</td>
</tr>
<tr>
<td>• Pneumonia</td>
<td>(this equates to approximately 6 mg/kg body weight) every 12 hours for 3 administrations</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>• Complicated urinary tract infections</td>
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<tr>
<td>• Bone and joint infections</td>
<td>800 mg IV</td>
<td>$&gt;20 \text{mg/L}^1$</td>
<td>12 mg/kg body weight IV or IM once a day</td>
<td>$&gt;20 \text{mg/L}^1$</td>
</tr>
<tr>
<td></td>
<td>(this equates to approximately 12 mg/kg body weight) every 12 hours for 3 to 5 administrations</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
• Infective endocarditis

| 800 mg intravenous (this equates to approximately 12 mg/kg body weight) every 12 hours for 3 to 5 administrations | 30–40 mg/L^1 | 12 mg/kg body weight intravenous or intramuscular once a day | >30 mg/L^1 |

^1 Measured by FPIA

The dose is to be adjusted for body weight whatever the weight of the patient.

**Duration of Treatment**

The duration of treatment should be decided based on the clinical response of the patient. For infective endocarditis, a minimum of 21 days is usually considered appropriate. Treatment should not exceed 4 months.

**Combination Therapy**

Teicoplanin has a limited spectrum of antibacterial activity (Gram-positive). It is not suitable for use as a single agent for the treatment of some types of infections unless the pathogen is already documented and known to be susceptible or there is a high suspicion that the most likely pathogen(s) would be suitable for treatment with teicoplanin.

**Method of Preparation**

Add 3 mL of Sterile Water for Injections IP to reconstitute the vial of teicoplanin and roll the vial gently until the powder is completely dissolved, taking care to avoid formation of foam. If the solution does become foamy, then allow to stand for about 15 minutes for the foam to subside.

It is important that the solution is correctly prepared and carefully withdrawn into the syringe; preparations that are not carefully executed can lead to the administration of less than 50% of the dose.

The concentration of a carefully prepared solution will be 100 mg in 1.5 mL (from the 200 mg vial) and 400 mg in 3 mL (from 400 mg vial).

The final solution is isotonic with a pH of 7.5. A calculated excess is included in each vial of TICOCSIN so that, when prepared as described above, a full dose of 200 mg or 400 mg (depending on the strength of the vial) will be obtained if all the reconstituted solution is withdrawn from the vial via a syringe.

The reconstituted solution may be injected directly or, alternatively, diluted with any of the following: 0.9% Sodium Chloride Injection, Compound Sodium Lactate Injection (Ringer-Lactate solution, Hartmann’s solution), 5% Dextrose Injection, 0.18% Sodium Chloride and 4% Dextrose Injection; Peritoneal dialysis solution containing 1.36% or 3.86% Dextrose.

**Method of Administration**

Teicoplanin should be administered by the IV or IM route.

The IV injection may be administered either as a bolus over 3 to 5 minutes or as a 30-minute infusion. Only the infusion method should be used in neonates.

**Special Populations**

**Geriatric**

No dose adjustment is required, unless there is renal impairment (see below).

**Renal Impairment**

Dose adjustment is not required until the fourth day of treatment, at which time dosing should be adjusted to maintain a serum trough concentration of at least 10 mg/L when measured by HPLC, or at least 15 mg/L when measured by the FPIA method.

**After the fourth day of Treatment**
In Mild and Moderate Renal Insufficiency (Creatinine Clearance 30-80 mL/min) Maintenance dose should be halved, either by administering the dose every two days or by administering half of this dose once a day.

In Severe Renal Insufficiency (Creatinine Clearance Less than 30 mL/min) and in Haemodialysed Patients Dose should be one third the usual dose, either by administering the initial unit dose every third day or by administering one third of this dose once a day.

Teicoplanin is not removed by haemodialysis.

**Patients undergoing CAPD**

After a single IV loading dose of 6 mg/kg body weight, 20 mg/L is administered in the bag of the dialysis solution in the first week, 20 mg/L in different bags the second week, and then 20 mg/L in the overnight bag in the third week.

**Paediatric**

The dose recommendations are the same in adults and children above 12 years of age.

**Neonates and Infants up to the Age of 2 Months**

*Loading Dose*

One single dose of 16 mg/kg body weight, administered intravenously by infusion on the first day.

*Maintenance Dose*

One single dose of 8 mg/kg body weight administered intravenously by infusion once a day.

**Children (Aged 2 months to 12 years)**

*Loading Dose*

One single dose of 10 mg/kg body weight administered intravenously every 12 hours, repeated 3 times.

*Maintenance Dose*

One single dose of 6-10 mg/kg body weight administered intravenously once a day.

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**Contraindications**

Hypersensitivity to teicoplanin or to any of the excipients.

**Warnings And Precautions**

**General**

**Hypersensitivity Reactions**

Serious, life-threatening hypersensitivity reactions, sometimes fatal, have been reported with teicoplanin (e.g. anaphylactic shock). If an allergic reaction to teicoplanin occurs, treatment should be discontinued immediately and appropriate emergency measures should be initiated.

Teicoplanin must be administered with caution in patients with known hypersensitivity to vancomycin, as crossed hypersensitivity reactions, including fatal anaphylactic shock, may occur.

However, a prior history of “red man syndrome” with vancomycin is not a contraindication to the use of teicoplanin.

**Infusion-related Reactions**

In rare cases (even at the first dose), red man syndrome (a complex of symptoms, including pruritus, urticaria, erythema, angioneurotic oedema, tachycardia, hypotension and dyspnoea) has been observed. Stopping or slowing the infusion may result in cessation of these reactions. Infusion-related reactions can be limited if the daily dose is not given via bolus injection but infused over a 30-minute period.

**Severe Bullous Reactions**

Life-threatening or even fatal cutaneous reactions, Stevens-Johnson syndrome (SJS) and toxic epidermal
necrolysis (TEN) have been reported with the use of teicoplanin. If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, teicoplanin treatment should be discontinued immediately.

**Spectrum of Antibacterial Activity**

Teicoplanin has a limited spectrum of antibacterial activity (Gram-positive). It is not suitable for use as a single agent for the treatment of some types of infections unless the pathogen is already documented and known to be susceptible or there is a high suspicion that the most likely pathogen(s) would be suitable for treatment with teicoplanin.

The rational use of teicoplanin should take into account the bacterial spectrum of activity, the safety profile and the suitability of standard antibacterial therapy to treat the individual patient. On this basis, it is expected that in most instances teicoplanin will be used to treat severe infections in patients for whom standard antibacterial activity is considered to be unsuitable.

**Loading Dose Regimen**

Since data on safety are limited, patients should be carefully monitored for adverse reactions when teicoplanin doses of 12 mg/kg body weight twice a day are administered. Under this regimen blood creatinine values should be monitored in addition to the recommended periodic haematological examination. Teicoplanin should not be administered by intraventricular use.

**Thrombocytopenia**

Thrombocytopenia has been reported with teicoplanin. Periodic haematological examinations are recommended during treatment, including complete cell blood count.

**Nephrotoxicity**

Renal failure has been reported in patients treated with teicoplanin. Patients with renal insufficiency, and/or in those receiving teicoplanin in conjunction with or sequentially with other medicinal products with known nephrotoxic potential (aminoglycosides, colistin, amphotericin B, ciclosporin, and cisplatin) should be carefully monitored, and should include auditory tests.

Since teicoplanin is mainly excreted by the kidneys, the dose of teicoplanin must be adapted in patients with renal impairment.

**Ototoxicity**

As with other glycopeptides, ototoxicity (deafness and tinnitus) has been reported in patients who develop signs and symptoms of impaired hearing or disorders of the inner ear during treatment with teicoplanin should be carefully evaluated and monitored, especially in case of prolonged treatment and in patients with renal insufficiency. Patients receiving teicoplanin in conjunction with or sequentially with other medicinal products with known neurotoxic/ototoxic potential (aminoglycosides, ciclosporin, cisplatin, furosemide and ethacrynic acid) should be carefully monitored and the benefit of teicoplanin evaluated if hearing deteriorates.

Special precautions must be taken when administering teicoplanin in patients who require concomitant treatment with ototoxic and/or nephrotoxic medicinal products for which it is recommended that regular haematology, liver and kidney function tests are carried out.

**Superinfection**

As with other antibiotics, the use of teicoplanin, especially if prolonged, may result in overgrowth of nonsusceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken.

**Drug Interactions**

No specific interaction studies have been performed. Teicoplanin and aminoglycoside solutions are incompatible and must not be mixed for injection; however, they are compatible in dialysis fluid and may be freely used in the treatment of CAPD-related peritonitis.
Teicoplanin should be used with care in conjunction with or sequentially with other medicinal products with known nephrotoxic or ototoxic potential. These include aminoglycosides, colistin, amphotericin B, ciclosporin, cisplatin, furosemide, and ethacrynic acid. However, there is no evidence of synergistic toxicity in combinations with teicoplanin.

In clinical studies, teicoplanin has been administered to many patients already receiving various medications, including other antibiotics, antihypertensives, anaesthetic agents, cardiac medicinal products and antidiabetic agents, without evidence of adverse interaction.

Renal Impairment

Please refer to DOSAGE AND ADMINISTRATION.

Pregnancy

There are limited amount of data from the use of teicoplanin in pregnant women. Studies in animals have shown reproductive toxicity at high doses in rats there was an increased incidence of stillbirths and neonatal mortality. The potential risk for humans is unknown. Therefore, teicoplanin should not be used during pregnancy unless clearly necessary. A potential risk of inner ear and renal damage to the foetus cannot be excluded.

Lactation

It is unknown whether teicoplanin is excreted in human milk. There is no information on the excretion of teicoplanin in animal milk. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with teicoplanin should be made taking into account the benefit of breastfeeding to the child and the benefit of teicoplanin therapy to the mother.

Fertility

Animal reproduction studies have not shown evidence of impairment of fertility.

Paediatric Use

Please refer to DOSAGE AND ADMINISTRATION.

Effects on Ability to Drive and Use Machines

Teicoplanin can cause dizziness and headache. The ability to drive or use machines may be affected. Patients experiencing these undesirable effects should not drive or use machines.

Undesirable Effects

Tabulated List of Adverse Reactions

In the table below, all the adverse reactions, which occurred at an incidence greater than placebo and more than one patient are listed using the following convention:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Adverse reactions should be monitored when teicoplanin doses of 12 mg/kg body weight twice a day are administered.

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1,000 to &lt;1/100)</th>
<th>Rare (≥1/10,000 to &lt;1/1,000)</th>
<th>Very rare (&lt;1/10,000)</th>
<th>Not known (cannot be estimated from available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Abscess</td>
<td>Superinfection (overgrowth of non-susceptible organisms)</td>
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<td></td>
<td></td>
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<td>-----------------------------</td>
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<td>-----------------------------------------------------</td>
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<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Leucopenia, thrombocytopenia, eosinophilia</td>
<td>Agranulocytosis, neutropenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Anaphylactic reaction (anaphylaxis)</td>
<td>Drug reaction with eosinophilia and systemic symptoms (DRESS), anaphylactic shock</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness, headache</td>
<td>Seizures</td>
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<td></td>
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<tr>
<td>Ear and labyrinth disorders</td>
<td>Deafness, hearing loss, tinnitus, vestibular disorder</td>
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<tr>
<td>Vascular disorders</td>
<td>Phlebitis</td>
<td>Thrombophlebitis</td>
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<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Bronchospasm</td>
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<tr>
<td>Gastro-intestinal disorders</td>
<td>Diarrhoea, vomiting, nausea</td>
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<td></td>
<td></td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash, erythema, pruritus</td>
<td>Red man syndrome (e.g. flushing of the upper part of the body)</td>
<td>Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, angio-oedema, dermatitis exfoliative, urticaria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Blood creatinine increased</td>
<td>Renal failure (including renal failure acute)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Pain, pyrexia</td>
<td>Injection site abscess, chills (rigors)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Investigations

Transaminases increased (transient abnormality of transaminases), blood alkaline phosphatase increased (transient abnormality of alkaline phosphatase), blood creatinine increased (transient rise of serum creatinine)

If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@Cipla.com. You can also report side effects directly via the National Pharmacovigilance Programme of India by calling on 1800 180 3024.

By reporting side effects, you can help provide more information on the safety of this product.

**Overdosage**

**Symptoms**

Cases of accidental administration of excessive doses to paediatric patients have been reported. In one case, agitation occurred in a 29-day old newborn who had been administered 400 mg intravenously (95 mg/kg).

**Management**

Treatment of teicoplanin overdose should be symptomatic. Teicoplanin is not removed by haemodialysis and only slowly by peritoneal dialysis.

**Incompatibility**

Teicoplanin and aminoglycoside are incompatible when mixed directly and must not be mixed before injection.

If teicoplanin is administered in combination therapy with other antibiotics, the preparation must be administered separately.

This medicinal product must not be mixed with other medicinal products except those mentioned under DOSAGE AND ADMINISTRATION.

**Shelf-Life**

See on the pack.

**Storage And Handling Instructions**

**Before opening**

Store below 25°C.
After reconstitution

In keeping with good clinical pharmaceutical practices, reconstituted vials of TICOCIN should be used immediately and any unused portion discarded. On the few occasions when this may be impractical due to other circumstances, the reconstituted solution should be kept at 2° to 8°C and discarded within 24 hours. Do not store in a syringe.

Packaging Information

TICOCIN-200 and TICOCIN-400: Available in vials of 10 mL.

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TICOCIN Injection

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