NEW ZEALAND DATA SHEET

Timentin® injection powder
Ticarcillin disodium/Potassium clavulanate

Presentation

TIMENTIN 3.1g vials: Each vial contains sterile ticarcillin disodium equivalent to 3g ticarcillin and sterile potassium clavulanate equivalent to 0.1g clavulanic acid.

TIMENTIN is supplied as a white to pale yellow powder for reconstitution.

TIMENTIN is very soluble in water; its solubility being greater than 600mg/mL. The reconstituted solution is clear, colourless or pale yellow, having a pH of 5.5 to 7.5.

The theoretical sodium content is 4.8mEq (111mg) per gram of TIMENTIN.

+ 

Indications

TIMENTIN is indicated in the treatment of infections caused by susceptible strains of organisms in the conditions listed below:

- Septicaemia (including bacteraemia)
- Lower Respiratory Tract Infections
- Bone and Joint Infections
- Skin and Skin Structure Infections
- Urinary Tract Infections
- Gynaecological Infections
- Surgical Prophylaxis

Appropriate culture and susceptibility tests should be performed in order to isolate and identify organisms causing infection and to determine their susceptibility to TIMENTIN. Susceptibility to TIMENTIN will vary with geography and time and local susceptibility data should be consulted where available (see Further Information, Pharmacodynamic properties).

In certain infections, when the causative organisms are unknown, TIMENTIN may be administered in conjunction with an aminoglycoside as initial therapy. As soon as results of culture and susceptibility tests become available, antimicrobial therapy should be adjusted as indicated.

TIMENTIN may be administered perioperatively (preoperatively, intraoperatively and postoperatively) to patients undergoing vaginal hysterectomy, abdominal surgery, and colorectal surgery when there is a significant risk of postoperative infection or where occurrence of postoperative infection is considered to be especially serious.
In patients undergoing caesarean section, intraoperative (after clamping the umbilical cord) and postoperative use of TIMENTIN may reduce the incidence of surgery related postoperative infections.

Effective prophylactic use depends on the time of administration. TIMENTIN usually should be given one half to one hour before the operation.

Prophylactic administration of TIMENTIN should usually be stopped within 24 hours since the continued administration of any antibiotic increases the possibility of adverse reactions, while in the majority of surgical procedures, it does not reduce the incidence of subsequent infection.

If signs of postsurgical infection should appear, specimens for culture should be obtained for identification of the causative organism(s) so that appropriate therapy may be instituted.

**Dosage and Administration**

The usual recommended dosage for average (60kg) adults is 3.1g (3.1g vial containing 3g ticarcillin and 100mg clavulanic acid) every 4 to 6 hours. For patients weighing less than 60kg, the recommended dosage is 200-300mg/kg/day, based on ticarcillin content, given in divided doses every 4 or 6 hours.

For infections complicated by renal insufficiency, an initial loading dose of 3.1g should be followed by doses based on creatinine clearance and type of dialysis as indicated below:

<table>
<thead>
<tr>
<th>Creatinine Clearance</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over 60</td>
<td>3.1g every 4 hours</td>
</tr>
<tr>
<td>30 - 60</td>
<td>2g (based on ticarcillin content) every 4 hours</td>
</tr>
<tr>
<td>10 - 30</td>
<td>2g (based on ticarcillin content) every 8 hours</td>
</tr>
<tr>
<td>Less than 10</td>
<td>2g (based on ticarcillin content) every 12 hours</td>
</tr>
<tr>
<td>Less than 10 with hepatic dysfunction</td>
<td>2g (based on ticarcillin content) every 24 hours</td>
</tr>
<tr>
<td>Patients on peritoneal dialysis</td>
<td>3.1g every 12 hours</td>
</tr>
<tr>
<td>Patients on haemodialysis</td>
<td>2g (based on ticarcillin content) every 12 hours supplemented with 3.1g after each dialysis</td>
</tr>
</tbody>
</table>

The half-life of ticarcillin in patients with renal failure is approximately 13 hours.

To calculate creatinine clearance* from a serum creatinine value use the following formula.

\[
C_{cr} = \frac{(140 - \text{Age})(\text{wt in kg})}{72 \times S_{cr} (\text{mg} \ 100\text{mL})}
\]

This is the calculated creatinine clearance for adult males, for females it is 15% less.


Dosage for any individual patient must take into considerations the site and severity of infection, the susceptibility of the organisms causing infection, and the status of the patient's host defence mechanisms.

The duration of therapy depends upon the severity of infection. Generally TIMENTIN should be continued for at least 2 days after the signs and symptoms of infection have disappeared. The usual duration is 10 to 14 days; however, in difficult and complicated infections, more prolonged therapy may be required.
For prophylactic use, the following dosages are recommended:
For patients undergoing caesarean section, the first dose of 3.1g is administered intravenously as soon as the umbilical cord is clamped. This is to be followed by 2 additional doses of 3.1g every 4 hours after the first dose for a total of 3 doses.

For patients undergoing abdominal hysterectomy, a dose of 3.1g administered half to one hour prior to the initial incision followed by 2 additional doses of 3.1g every 4 hours for a total of 3 doses.

For patients undergoing abdominal surgery or colorectal surgery, a dose of 3.1g administered intravenously half to one hour prior to the initial incision followed by 2 additional doses of 3.1g every 4-6 hours for a total of 3 doses.

Frequent bacteriologic and clinical appraisal is necessary during therapy of chronic urinary tract infection and may be required for several months after therapy has been completed; persistent infections may require treatment for several weeks and doses smaller than those indicated above should not be used.

In certain infections, involving abscess formation, appropriate surgical drainage should be performed in conjunction with antimicrobial therapy.

Children (2 - 12 years): The daily dose for children should not exceed the adult dosage. The usual recommended dosage for systemic and urinary tract infections is 200 to 300mg/kg/day based on ticarcillin content, given intravenously in divided doses every 4 to 6 hours.
Children under 2 years and neonates: Insufficient data are available to make a dosage recommendation for this group.

Intravenous Infusion:
The 3.1g vial should be reconstituted by shaking with 20mL of Sterile Water for Injection, Sodium Chloride Injection or Sodium Lactate Injection; when dissolved, the concentration of ticarcillin will be approximately 140mg/mL with a corresponding concentration of 4.5mg/mL clavulanic acid.

Conversely, each 7.4mL of the 3.1g dose reconstituted with 20mL of diluent will contain approximately 1g of ticarcillin and 33mg of clavulanic acid.

Alternatively, stock solutions of approximately 200mg/mL and 400mg/mL (based on ticarcillin content) may be prepared by reconstituting the vials with 12mL and 6mL of diluent, respectively.

The dissolved medicine should be further diluted to desired volume using a suitable solution listed below (see Pharmaceutical Particulars). The solution of reconstituted medicine may then be administered over a period of 30 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place. If this method or the "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of TIMENTIN.

When TIMENTIN is given in combination with another antimicrobial, such as an aminoglycoside, each medicine should be given separately in accordance with the recommended dosage and routes of administration for each medicine. After reconstitution and prior to administration, TIMENTIN, as with other parenteral medicines, should be inspected visually for particulate matter with discolouration.

Contraindications

TIMENTIN contains ticarcillin which is a penicillin, and should not be given to patients with a history of hypersensitivity to beta-lactam antibiotics (eg. penicillins and cephalosporins).
Warnings and Precautions

Before initiating therapy with TIMENTIN, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactams (eg. penicillins and cephalosporins).

Serious and occasionally fatal hypersensitivity reactions (anaphylaxis) have been reported in patients receiving beta-lactam antibiotics. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral therapy.

These reactions are more likely to occur in individuals with a history of beta-lactam hypersensitivity. If an allergic reaction occurs, the drug should be discontinued and the appropriate therapy instituted. Serious anaphylactoid reactions require immediate emergency treatment with adrenaline. Oxygen, intravenous steroids, and airway management, including intubation, may also be required.

While TIMENTIN possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function is advisable during prolonged therapy.

Bleeding manifestations have occurred in some patients receiving beta-lactam antibiotics. These reactions have been associated with abnormalities of coagulation tests such as clotting time, platelet aggregation and prothrombin time and are more likely to occur in patients with renal impairment. If bleeding manifestations appear, TIMENTIN treatment should be discontinued and appropriate therapy instituted.

TIMENTIN has only rarely been reported to cause hypokalaemia; however, the possibility of this occurring should be kept in mind particularly when treating patients with fluid and electrolyte imbalance. Periodic monitoring of serum potassium may be advisable in patients receiving prolonged therapy.

TIMENTIN contains sodium (see Presentation for sodium content). This should be included in the daily allowance of patients on sodium restricted diets.

Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

Pseudomembranous colitis has been reported with the use of antibiotics and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhoea during or after antibiotic use. If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further.

In patients with renal impairment, dosage should be adjusted according to the degree of impairment (see Posology and method of administration).

Use in Pregnancy:
Animal studies with TIMENTIN have shown no teratogenic effects. Penicillins are generally considered safe for use in pregnancy. Limited information is available concerning the results of the use of TIMENTIN in human pregnancy. The decision to administer any drug during pregnancy should be taken with the utmost care. Therefore TIMENTIN should only be used in pregnancy when the potential benefits outweigh the potential risks associated with treatment.

Use in Lactation:
Trace quantities of TIMENTIN are excreted in breast milk.
TIMENTIN may be administered during the period of lactation. With the exception of the risk of sensitization, there are no detrimental effects for the breast-fed infant.

**Effects on Ability to Drive and Use Machines**
Adverse effects on the ability to drive or operate machinery have not been observed.

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**Adverse Effects**

**Hypersensitivity reactions:**
Hypersensitivity effects, including: Skin rashes, pruritus, urticaria, and anaphylactic reactions. Bullous reactions (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis) have been reported very rarely.

**Gastrointestinal effects:**
Nausea, vomiting and diarrhoea have been reported. Pseudomembranous colitis has been reported rarely (See Warnings and Precautions).

**Hepatic effects:**
A moderate rise in AST and/or ALT has been noted in patients treated with beta-lactam class antibiotics, but the significance of these findings is unknown. Hepatitis and cholestatic jaundice have been reported very rarely. These events have been noted with other penicillins and cephalosporins.

**Renal and urinary effects:**
Hypokalaemia has been reported rarely. Haemorrhagic cystitis has been reported very rarely.

**Central Nervous System effects:**
Convulsions may occur rarely, particularly in patients with impaired renal function or in those receiving high doses.

**Haematological effects:**
Thrombocytopenia, leukopenia and eosinophilia have been reported rarely and reduction of hemoglobin. Prolongation of prothrombin time and bleeding time. Bleeding manifestations have occurred.

**Local effects:**
Pain, burning, swelling and induration at the injection site and thrombophlebitis with intravenous administration.

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**Interactions**

Co-administration of probenecid cannot be recommended. Probenecid decreases the renal tubular secretion of ticarcillin. Concurrent administration of probenecid delays ticarcillin renal excretion but does not delay the excretion of clavulanic acid.

The presence of clavulanic acid in TIMENTIN may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

In common with other antibiotics, ticarcillin may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.
**Overdose**

Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident and should be treated symptomatically.

Disturbances of the fluid and electrolyte balances may be evident and may be treated symptomatically.

Ticarcillin and clavulanic acid may be removed from circulation by haemodialysis.

As with other penicillins, TIMENTIN overdosage has the potential to cause neuromuscular hyperirritability or convulsive seizures.

**Further information**

**Actions**

TIMENTIN is an injectable antibacterial combination consisting of the semisynthetic antibiotic, ticarcillin disodium and the beta-lactamase inhibitor, clavulanate potassium (the potassium salt of clavulanic acid) for intravenous administration.

Ticarcillin is a semisynthetic antibiotic with a broad spectrum of bactericidal activity against many Gram-positive and Gram-negative aerobic and anaerobic bacteria.

Ticarcillin is derived from the basic penicillin nucleus, 6-amino-penicillanic acid.

Ticarcillin is, however, susceptible to degradation by beta-lactamases and therefore the spectrum of activity does not normally include organisms which produce these enzymes.

Clavulanic acid is produced by the fermentation of *Streptomycyes Clavuligerus*. It is a beta-lactam structurally related to the penicillins and possesses the ability to inactivate a wide variety of beta-lactamases by blocking the active sites of these enzymes. Clavulanic acid is particularly active against the clinically important plasmid mediated beta-lactamases frequently responsible for transferred drug resistance to penicillins and cephalosporins.

The formulation of ticarcillin with clavulanic acid in TIMENTIN protects ticarcillin from degradation by beta-lactamase enzymes and effectively extends the antibiotic spectrum of ticarcillin to include many bacteria normally resistant to ticarcillin and other beta-lactam antibiotics. Thus TIMENTIN possesses the distinctive properties of a broad spectrum antibiotic and a beta-lactamase inhibitor.

**Pharmacodynamic properties**

The prevalence of acquired resistance is geographically and time dependent and for select species may be very high. Local information on resistance is desirable, particularly when treating severe infections.

In vitro susceptibility of micro-organisms to Ticarcillin/Clavulanate

Where clinical efficacy of ticarcillin/clavulanic acid has been demonstrated in clinical trials this is indicated with an asterisk (*).

Organisms that do not produce beta-lactamase are identified (with †). If an isolate is susceptible to ticarcillin, it can be considered susceptible to ticarcillin/clavulanate.
### Commonly Susceptible Species

<table>
<thead>
<tr>
<th>Gram-positive aerobes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus (methicillin-susceptible isolates only)*</td>
</tr>
<tr>
<td>Staphylococcus epidermidis (methicillin-susceptible isolates only)*</td>
</tr>
<tr>
<td>Staphylococcus saprophyticus</td>
</tr>
<tr>
<td>Beta-hemolytic streptococci†</td>
</tr>
<tr>
<td>Streptococcus bovis†</td>
</tr>
<tr>
<td>Enterococcus faecalis†</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gram-positive aerobes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moraxella catarrhalis</td>
</tr>
<tr>
<td>Pasteurella multocida</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Gram-positive anaerobes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clostridium spp.</td>
</tr>
<tr>
<td>Eubacterium spp.</td>
</tr>
<tr>
<td>Peptostreptococcus spp.†</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gram-negative aerobes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteroides spp. including B. fragilis</td>
</tr>
<tr>
<td>Prevotella spp.</td>
</tr>
<tr>
<td>Fusobacterium spp.</td>
</tr>
</tbody>
</table>

### Species for which acquired resistance may be a problem

<table>
<thead>
<tr>
<th>Gram-positive aerobes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pneumoniae†</td>
</tr>
<tr>
<td>Viridans group streptococci†</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Gram-negative aerobes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter spp.</td>
</tr>
<tr>
<td>Citrobacter spp.†</td>
</tr>
<tr>
<td>Enterobacter spp.†</td>
</tr>
<tr>
<td>Escherichia coli†</td>
</tr>
<tr>
<td>Haemophilus influenzae*</td>
</tr>
<tr>
<td>Klebsiella spp.†</td>
</tr>
<tr>
<td>Morganella morganii</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
</tr>
<tr>
<td>Proteus spp.</td>
</tr>
<tr>
<td>Providencia spp.</td>
</tr>
<tr>
<td>Pseudomonas spp.† including Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>Serratia spp.†</td>
</tr>
<tr>
<td>Salmonella spp.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gram-negative anaerobes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veillonella spp.</td>
</tr>
</tbody>
</table>

### Inherently Resistant Organisms

| Stenotrophomonas maltophilia |
| Burkholderia cepacia |

### Activity:

Clavulanic acid is a beta-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of beta-lactamase enzymes commonly found in microorganisms resistant to
penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid mediated beta-lactamases frequently responsible for transferred drug resistance.

**Pharmacokinetics**

After an intravenous infusion (30 minutes) of TIMENTIN, ticarcillin serum levels are similar to those produced by the administration of equivalent amounts of ticarcillin alone. The mean serum pharmacokinetic parameters are listed below:

<table>
<thead>
<tr>
<th>Dose</th>
<th>Ticarcillin</th>
<th>Clavulanic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt; (µg/mL)</td>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
</tr>
<tr>
<td>3.1 g</td>
<td>324</td>
<td>0.5</td>
</tr>
<tr>
<td>3.2 g</td>
<td>336</td>
<td>0.5</td>
</tr>
<tr>
<td>3.1 g</td>
<td>8.0</td>
<td>0.5</td>
</tr>
<tr>
<td>3.2 g</td>
<td>15.8</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Somewhat higher and more prolonged serum levels of ticarcillin can be achieved with the concurrent administration of probenecid; however, probenecid does not enhance the serum levels of clavulanic acid.

**Distribution:**

Ticarcillin can be detected in tissues and interstitial fluid following parenteral administration. Penetration of ticarcillin into the bile, pleural fluid and cerebrospinal fluid with inflamed meninges has been demonstrated. The results of experiments involving the administration of clavulanic acid to animals suggest that this compound, like ticarcillin, is well distributed in body tissues. An inverse relationship exists between the serum half-life of ticarcillin and creatinine clearance. The dosage of 'TIMENTIN' need only be adjusted in cases of severe renal impairment (see Dosage and Administration). Ticarcillin may be removed from patients undergoing dialysis; the actual amount removed depends on the duration and type of dialysis.

**Protein binding:**

Neither component of 'TIMENTIN' is highly protein bound; ticarcillin has been found to be approximately 50% bound to human serum protein and clavulanic acid approximately 25% bound.

**Elimination:**

The mean serum half-life of ticarcillin and clavulanic acid in healthy volunteers is 68 minutes. Approximately 60-70% of ticarcillin and approximately 35-45% of clavulanic acid are excreted unchanged in urine during the first hours after administration of a single dose of 'TIMENTIN' to normal volunteers with normal renal function. Two hours after an intravenous injection of 3.1g 'TIMENTIN', concentrations of ticarcillin in urine generally exceed 1500mcg/mL. The corresponding concentrations of clavulanic acid in urine generally exceed 40mcg/mL. By 4-6 hours after injection, the urine concentrations of ticarcillin and clavulanic acid usually decline to approximately 190mcg/mL.

**Preclinical safety data**

No further information of clinical relevance.
Pharmaceutical Precautions

Instructions for Handling
When TIMENTIN is given in combination with another antimicrobial, such as an aminoglycoside, each drug should be given separately in accordance with the recommended dosage and routes of administration for each drug.

Administration Instructions
Shake the vial/bottle and solvent well to ensure complete dissolution.
If administering by "piggyback" or infusion method, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of TIMENTIN.

INTRAVENOUS INFUSION
Dilute the above solution to the desired concentration (10-100mg/mL). Administer over 30 minutes.

3.1g vial (dilution derived from a stock solution of 200mg/mL)
The concentrated stock solution at 200mg/mL is stable for up to 6 hours at room temperature (21-24°C) or up to 72 hours under refrigeration (4°C).

If the concentrated stock solution (200mg/mLl) is held for up to 6 hours at room temperature (21-24°C) or up to 72 hours under refrigeration (4°C) and further diluted to a concentration between 10mg/mL and 100mg/mL with any of the diluents listed below, then the following stability periods apply.

<table>
<thead>
<tr>
<th>STABILITY PERIOD:</th>
<th>Room Temperature (21-24°C)</th>
<th>Refrigerated (4°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous Solution (Ticarcillin</td>
<td>24 hours</td>
<td>3 days</td>
</tr>
<tr>
<td>Concentrations of 10mg/mL to 100mL)</td>
<td>24 hours</td>
<td>7 days</td>
</tr>
<tr>
<td>Dextrose Injection 5%, U.S.P.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium Chloride Injection U.S.P.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactated Ringer's Injection U.S.P.</td>
<td></td>
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</tr>
</tbody>
</table>

If the concentrated stock solution (200mg/mL) is stored for up to 6 hours at room temperature and then further diluted to a concentration between 10mg/mL and 100mg/mL, solutions of Sodium Chloride Injection, U.S.P., and Lactated Ringer's Injection, U.S.P. may be stored frozen (-18°C) for up to 30 days. Solutions prepared with Dextrose Injection 5%, U.S.P. may be stored frozen (-18°C) for up to 7 days. All thawed solutions should be used within 8 hours or discarded. Once thawed, solutions should not be refrozen.

Incompatibilities
TIMENTIN is incompatible with Sodium Bicarbonate.
TIMENTIN solutions containing lignocaine hydrochloride should not be used for intravenous administration.
If prescribed concurrently with an aminoglycoside, the antibiotics should not be mixed in the syringe, intravenous fluid container or giving set because of loss of activity of the aminoglycoside under these conditions.

Shelf Life
TIMENTIN vials should be stored at room temperature or below for a maximum shelf life of 18 months at 25°C.

**Special Precautions for Storage**
The stock solutions are stable for 6 hours at room temperature or for 72 hours when stored under refrigeration (4°C).

TIMENTIN at concentrations up to 100mg/mL (based on ticarcillin content) in the following solutions will lose less than 10% activity over 24 hours when stored at room temperature: Sterile Water for Injections BP, Sodium Chloride Injection BP, Sodium Lactate Injection BP. Unused solutions should be discarded after the time period stated.

**Package Quantities**
TIMENTIN 3.1g vials are available in single vial packs.

**Medicines Schedule**
Prescription Only Medicine

**Sponsor Details**
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NEW ZEALAND

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Facsimile: (09) 367 2910

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Version: 3.0

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