APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S4

PROPRIETARY NAME (AND DOSAGE FORM):

TRYCOSIL 250 mg INJECTION (Sterile powder for solution for injection)

TRYCOSIL 500 mg INJECTION (Sterile powder for solution for injection)

TRYCOSIL 1 g INJECTION (Sterile powder for solution for injection)

COMPOSITION:

TRYCOSIL 250 mg INJECTION is available in vials containing the equivalent of 250 mg ampicillin as ampicillin sodium, presented as a powder for reconstitution. Each vial contains approximately 16.5 mg of sodium.

TRYCOSIL 500 mg INJECTION is available in vials containing the equivalent of 500 mg ampicillin as ampicillin sodium, presented as a powder for reconstitution. Each vial contains approximately 33 mg of sodium.

TRYCOSIL 1 g INJECTION is available in vials containing the equivalent of 1 g ampicillin as ampicillin sodium, presented as a powder for reconstitution. Each vial contains approximately 66 mg of sodium.

PHARMACOLOGICAL CLASSIFICATION:

A 20.1.2 Penicillins

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties

Ampicillin has in vitro bactericidal activity against a broad spectrum of non-penicillinase-producing gram-positive and gram-negative organisms. Ampicillin inhibits the bacterial cell wall from forming, by specifically inhibiting the activity of transpeptidase enzymes, which catalyse cross-linkage of the glycopeptide polymer unit that forms the cell wall.

In vitro sensitivity does not necessarily imply in vivo efficacy.

Resistant organisms:

Ampicillin is deactivated by beta lactamases. Most staphylococci and many strains of *E.coli*, *H.influenza*, *M.catarrhalis*, *N.gonorrhoeae*, *Salmonella* and *Shingella* spp. are resistant.

Pharmacokinetic properties:

Intramuscular injection of 0,5 or 1 g of sodium ampicillin yields peak plasma concentrations of about 7 or 10 micrograms per ml, respectively, at 1 hour; these decline exponentially, with a half-time of approximately 80 minutes. The half-life may be increased in neonates and the elderly; in renal impairment half-lives of 7 to 20 hours have been reported. Peritoneal dialysis is ineffective in removing ampicillin from the blood, but haemodialysis removes about 40 % of the body store in about 7 hours. Adjustment of the dose of ampicillin is required in the presence of renal dysfunction. Ampicillin appears in the bile, undergoes enterohepatic circulation, and is excreted in appreciable quantities in the faeces.
Ampicillin is metabolised to some extent to penicilloic acid which is excreted in the urine.
Renal clearance of ampicillin occurs partly by glomerular filtration and partly by tubular secretion.
Following parenteral administration about 60 to 80 % is excreted in the urine within 6 hours.
Ampicillin is widely distributed and therapeutic concentrations can be achieved in ascitic, pleural, and joint fluids. Ampicillin crosses the placenta into the foetal circulation and small amounts are distributed into breast milk. About 20 % is bound to plasma proteins and there is little diffusion into the CSF except when the meninges are inflamed.

INDICATIONS:

TRYCOSIL INJECTION is indicated for the treatment of bacterial infections caused by non-penicillinase-producing ampicillin-sensitive organisms. Parenteral usage is indicated where oral dosage is inappropriate.

CONTRA-INDICATIONS:

TRYCOSIL should not be given to:

- Patients known to be hypersensitive or allergic to penicillins such as ampicillin or cephalosporins (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).
- Babies in the neonatal period, born to mothers hypersensitive to ampicillin.

WARNINGS AND SPECIAL PRECAUTIONS:

Serious and occasionally fatal hypersensitivity (severe anaphylactic) reactions have been reported in patients on ampicillin/penicillin therapy. Before initiating therapy with **TRYCOSIL INJECTION**, careful enquiry should be made concerning previous hypersensitivity or allergic reactions to penicillins, cephalosporins or other allergies. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity that have experienced severe reactions when treated with cephalosporins.

Resuscitative equipment should be available when **TRYCOSIL INJECTION** is to be administered, and patients should be observed for at least one hour after administration of **TRYCOSIL INJECTION**.

If an allergic reaction occurs, **TRYCOSIL INJECTION** should be discontinued and the appropriate therapy instituted. Serious anaphylactic reactions may require immediate emergency treatment with epinephrine (adrenaline), oxygen, intravenous steroids, anti-histamines and airway management, including intubation.

TRYCOSIL INJECTION should be used with caution in patients with known history of allergy.

Caution is needed when administering **TRYCOSIL INJECTION** to patients with syphilis as the Jarisch-Herxheimer reaction may occur shortly after commencing treatment in these patients. This reaction, which manifests in fever, chills, headache and reactions at the site of the lesion, may be dangerous in cardiovascular syphilis or where there is a serious risk of increased local damage such as with optic atrophy.

TRYCOSIL INJECTION should be discontinued if a skin rash occurs. It should preferably be avoided if infectious mononucleosis, lymphatic leukemia or possibly HIV infection is suspected and also in patients receiving allopurinol treatment, because of an increased risk of rashes associated with these conditions, following the administration of **TRYCOSIL INJECTION**.

When high doses are administered, adequate fluid intake and urinary output must be maintained.

The use of lidocaine together with TRYCOSIL INJECTION should be considered only when administering an intramuscular injection, and must not be given intravenously.

Prolonged use may result in overgrowth of non-susceptible organisms. Antibiotic- associated pseudomembranous enterocolitis has been reported, with ampicillin contained in **TRYCOSIL INJECTION**.

It may range in severity from mild to life threatening. Therefore it is important to consider this side- effect in patients who present with diarrhoea during or subsequent to administration of **TRYCOSIL INJECTION**.

Increases in the INR have been reported in patients receiving **TRYCOSIL INJECTION**. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently.

Periodic assessment of organ function, including renal, hepatic and haematopoietic functions, is advisable during prolonged therapy.

TRYCOSIL INJECTION should not be mixed in the same syringe or administration set with aminoglycosides such as gentamycin, or with other beta-lactam antibacterials such as cephalosporins (see **"INTERACTIONS"**).

Do not add to containers of infusions containing dextrose. It may be piggybacked via the same administration set.

High doses of sodium penicillins such as **TRYCOSIL INJECTION** may cause hypokalaemia and sometimes hypernatraemia. Use of a potassium sparing diuretic may be helpful.

Care should be taken when high doses of **TRYCOSIL INJECTION** are given to patients with renal impairment (due to the risk of neurotoxicity) or congestive heart failure. In the presence of impaired renal function large doses of **TRYCOSIL INJECTION** (e.g. more than 8 g per day in an adult) may cause cerebral irritation, convulsions and coma.

Renal systems should be monitored during prolonged and high dose therapy. When high doses are administered, adequate fluid intake and urinary output must be maintained.

Contact with **TRYCOSIL INJECTION** should be avoided since skin sensitisation may occur.

The sodium content must be taken into account in patients on a sodium-restricted diet if the administration of high doses is necessary as each gram of ampicillin sodium contains 2, 7mmol of sodium. If symptoms due to overgrowth of non-susceptible organisms such as *Aerobacter*, *Pseudomonas*, or *Candida* species appear, **TRYCOSIL INJECTION** should be discontinued and supportive therapy instituted.

There have been reports of paraesthesia following long-term administration. **The use of lidoocaine**

together with TRYCOSIL INJECTION should be considered only when administering an intramuscular injection, and must not be given intravenously.

Intrathecal administration of **TRYCOSIL INJECTION** is not used, since it may precipitate convulsions when given by this route.

Convulsions and other signs of toxicity to the central nervous system may occur particularly with intravenous administration, in those receiving high doses or in patients with impaired renal function or renal failure.

Ability to drive and operate machinery:

TRYCOSIL INJECTION may cause drowsiness. Caution must be exercised when driving or operating machinery.

INTERACTIONS:

TRYCOSIL INJECTION should not be mixed in the same syringe or administration set with aminoglycosides such as gentamycin, as substantial inactivation of the aminoglycosides may result, or with other beta-lactam antibacterials such as cephalosporins, as substantial mutual inactivation may result. If these groups of antibacterials are to be administered concurrently, they should be administered at separate sites, at least 1 hour apart (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

TRYCOSIL INJECTION markedly decreases the clearance of methotrexate given intravenously for the treatment of neoplasms, which may result in toxicity.The combination should be avoided or patients should be closely monitored; and leucovorin doses may need to be increased and administered for longer periods of time.

Concurrent use of **TRYCOSIL INJECTION** with ACE inhibitors, potassium-sparing diuretics, potassium-containing medications or potassium supplements may promote serum potassium accumulation with possible resultant hyperkalaemia, especially in patients with renal insufficiency; concurrent administration with ACE inhibitors may result in hyperkalaemia since reduction of aldosterone production induced by ACE inhibitors may lead to elevation of serum potassium.

Concurrent use of medication with an antiplatelet function with **TRYCOSIL INJECTION** may increase the risk of haemorrhage due to additive inhibition of platelet aggregation. In addition, hypoprothrombinaemia induced by large doses of salicylates, and the gastrointestinal ulcerative or haemorrhagic potential of

NSAIDs or salicylates may also increase the risk of haemorrhage when these medications are used concurrently with **TRYCOSIL INJECTION**.

Patients receiving anticoagulants, heparin or thrombolytic agents may experience a prolonged INR and bleeding following treatment with **TRYCOSIL INJECTION**.

TRYCOSIL INJECTION may reduce the efficacy of oral contraceptives and patients should be warned accordingly to use alternative or additional measures of contraception.

The concomitant administration of allopurinol and **TRYCOSIL INJECTION** substantially increases the incidence of skin rashes in patients receiving both agents as compared to patients receiving ampicillin alone. This is especially so for hyperuricaemic patients. It is not known whether this potentiation of rashes is due to allopurinol or the hyperuricaemia present in these patients.

No information is available about the concurrent use of **TRYCOSIL INJECTION** and alcohol. However, the ingestion of alcohol whilst being treated with some other beta-lactam antibiotics has precipitated a disulfiram-like reaction in some patients. Therefore, the ingestion of alcohol should be avoided during and for several days after treatment with **TRYCOSIL INJECTION**.

It is recommended that when testing for the presence of glucose in urine during treatment with **TRYCOSIL INJECTION**, enzymatic glucose oxidase methods should be used. Due to the high urinary concentrations of penicillins such as **TRYCOSIL INJECTION**, false positive or falsely elevated readings are common with chemical methods such as copper sulphate.

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established.

Animal studies with **TRYCOSIL INJECTION** have shown no teratogenic effects.

Use in lactation:

TRYCOSIL INJECTION are distributed into breast milk. The use of **TRYCOSIL INJECTION** by breast-feeding mothers may lead to sensitisation, diarrhoea, candidiasis and skin rash in the infant.

DOSAGE AND DIRECTIONS FOR USE:

Recommended Adult Dosage:

Adults (including elderly patients): 500 – 1000 mg 4 - 6 times a day intravenously for as long as IV therapy is required.

Meningitis: 2 g six-hourly intravenously. (Children's dosage: 150 mg/kg daily intravenously in 4 divided doses).

In the treatment of beta-haemolytic streptococcal infections, a therapeutic dose must be administered for at least 10 days.

The above dosages may be increased in particularly severe infections.

Children < 20 kg:

10 - 25 mg/kg 6 hourly.

Children ≥ 20 kg:

Adult dose.

Meningitis or severe infections:

50 mg/kg 6 hourly.

Neonates:

5 mg/kg/dose (meningitis: 100 mg/kg/dose) 12 hourly in the first week of life, and then 8 hourly in the second week. Then after the second week 1 - 3 mg/kg/dose 6 hourly.

Administration:

When prepared for intramuscular or direct intravenous injection, **TRYCOSIL INJECTION** should be administered immediately after reconstitution (see "**RECONSTITUTION AND STORAGE INSTRUCTIONS**").

Intramuscular: 250 mg, 500 mg, 1 g – add 1,0 to 3,5 ml Water for Injections.

Intravenous: Dissolve the contents of a vial in the specified volume of Water for Injections. 250 mg – 5,0 ml; 500 mg – 5,0 ml; 1 g – 7,4 ml.

The intravenous dose is given by slow injection (3-4 minutes). Alternatively it may also be added to infusion fluids or be injected, suitably diluted, into the drip tube over 3-4 minutes (refer to table under "**STABILITY**").

Intraperitoneal **:** Dialysis: 50 mg per litre of dialysate.

Therapeutic **:** Dissolve 500 mg in 5 to 10 ml Water for Injections.

Intrapleural **:** Dissolve 500 mg in 5 to 10 ml Water for Injections.

Intra-Articular **:** 50 - 100 mg/ml of Water for Injections or 0,5 % lignocaine hydrochloride to make up to volume of 2,5 ml.

Topical : Sprinkle 500 mg to 1 g dry powder extraperitoneally before closure and suturing.

Stability and Compatibility : Injectable solution : Only freshly prepared solution should be used (see reconstitution instructions).

Intravenous infusion: **TRYCOSIL INJECTION** is compatible with the following intravenous fluids, but solutions must be used within the periods shown below:

Table: Period of stability of TRYCOSIL INJECTION intravenous infusion solution at room temperature.

Sodium Chloride 0, 9 %	6 - 8 hours
5 % Dextrose	1 hour
Dextrose in sodium chloride 0, 9 %	1 hour
Ringer's lactate solution	6 - 8 hours
1, 4 % Sodium bicarbonate	4 hours

TRYCOSIL INJECTION should not be added to infusion bottles containing Dextran 40 Injection, but may be injected into the drip tubing of such an infusion.

Blood and Plasma: A dilute solution (i.e. 500 mg dissolved in 20 ml Water for Injection) should be injected slowly into the drip tubing rather than added to the infusion bottle.

Reconstitution and storage instructions:

Reconstitute the powder using a suitable sterile diluent.

The reconstituted product should be administered immediately after reconstitution.

Do not freeze.

NB: TRYCOSIL INJECTION VIALS ARE NOT SUITABLE FOR MULTIDOSE USE.

Discard any unused portion(s).

SIDE-EFFECTS

Immune system disorders:

If any hypersensitivity reaction occurs, treatment should be discontinued immediately.

Less frequent:

Severe allergic reactions including angioedema, anaphylaxis, serum sickness and vasculitis.

Skin rashes such as erythema multiforme and Stevens-Johnson syndrome, toxic epidermal necrolysis and bullous and exfoliative dermatitis and other skin rashes.

A generalised sensitivity reaction with urticaria, fever, joint pains and eosinophilia can develop within a few hours to several weeks after starting treatment.

Infections and infestations:

The following side-effects have been reported and frequencies are unknown:

Superinfection by resistant or non-susceptible species such as *Pseudomonas* or *Candida* or *Aerobacter* species.

Blood and the lymphatic system disorders:

Less frequent:

Leucopenia, thrombocytopenia, and coagulation disorders such as prolongation of bleeding time and defective platelet function.

The following side-effects have been reported and frequencies are unknown:

Haemolytic anaemia, granulocytopenia and agranulocytosis.

Haematological parameters should be monitored during prolonged and high dose therapy.

Investigations:

Increased sodium plasma concentrations with higher doses of **TRYCOSIL INJECTION**.

The following side-effects have been reported and frequencies are unknown:

Disturbances of blood electrolytes may follow administration of large doses of **TRYCOSIL INJECTION** and may interfere with some diagnostic tests, such as those for urinary glucose using copper sulphate, direct anti-globulin (Coombs') tests, and some tests for urinary or serum proteins. **TRYCOSIL INJECTION** may interfere with tests that use bacteria, for example the Guthrie test for phenylketonuria using *Bacillus subtilis* organisms.

Nervous system disorders:

Less frequent:

Convulsions. paraesthesia

The following side-effects have been reported and frequencies are unknown:

Hyperkinesia and dizziness.

Gastrointestinal disorders:

Frequent:

Nausea, vomiting and diarrhoea.

Less frequent:

Antibiotic-associated colitis (pseudomembranous colitis).

The following side-effects have been reported and frequencies are unknown:

Stomatitis, glossitis, black hairy tongue and heartburn.

Mucocutaneous candidiasis and antibiotic-associated colitis (haemorrhagic colitis)

Hepato-biliary disorders:

The following side-effects have been reported and frequencies are unknown:

A moderate rise in liver enzyme (aspartate transaminase (AST) and/or alanine transaminase (ALT) values. Hepatitis and cholestatic jaundice.

Skin and subcutaneous tissue disorders:

Frequent: Urticaria, skin rashes

Renal and urinary disorders:

The following side-effects have been reported and frequencies are unknown:

Crystalluria, interstitial nephritis.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Overdosage with ampicillins such as **TRYCOSIL INJECTION** is usually asymptomatic. Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident and symptoms of water and electrolyte imbalance should be treated symptomatically.

Adequate fluid intake and urinary output must be maintained to minimise the crystalluria.

TRYCOSIL INJECTION may be removed from the circulation by haemodialysis. Peritoneal dialysis is not effective in the removal thereof. Treatment is symptomatic and supportive (see **"SIDE-EFFECTS"**).

IDENTIFICATION:

TRYCOSIL 250 mg INJECTION: White to off - white powder filled in 10 ml clear glass vials, stoppered with grey butyl rubber stoppers and sealed with taxim blue colour flip off seals.

When reconstituted (including reconstitution for intramuscular use); a clear, colourless solution is formed.

TRYCOSIL 500 mg INJECTION: White to off - white powder filled in 10 ml clear glass vials, stoppered with grey butyl rubber stoppers and sealed with yellow colour flip off seals.

When reconstituted (including reconstitution for intramuscular use); a clear, colourless solution is formed.

TRYCOSIL 1 g INJECTION: White to off - white powder filled in 15 ml clear glass vials, stoppered with grey butyl rubber stoppers and sealed with dark green colour flip off seals.

When reconstituted (including reconstitution for intramuscular use); a clear, colourless solution is formed.

PRESENTATION:

TRYCOSIL 250 mg INJECTION: 10 ml Type-I moulded clear, colourless glass vials fitted with 20 mm grey colour bromo butyl rubber stoppers and sealed with 20 mm taxim blue colour flip off seal.

Pack size: Single dose vial packed in printed carton with a package insert.

TRYCOSIL 500 mg INJECTION: 10 ml Type-I moulded clear, colourless glass vials fitted with 20 mm grey colour bromo butyl rubber stoppers and sealed with 20 mm yellow colour flip off seal.

Pack size: Single dose vial packed in printed carton with a package insert.

TRYCOSIL 1 g INJECTION: 15 ml Type-I moulded clear, colourless glass vials fitted with 20 mm grey colour bromo butyl rubber stoppers and sealed with 20 mm dark green colour flip off seal.

Pack size: Single dose vial packed in printed carton with a package insert.

STORAGE INSTRUCTIONS:

Store at or below 25°C in a dry place. Protect from light.

The reconstituted product should be administered immediately after reconstitution.

Do not freeze.

KEEP OUT OF REACH OF CHILDREN.

Discard any unused portion(s).

REGISTRATION NUMBER:

TRYCOSIL 250 mg INJECTION: 45/20.1.2/0785

TRYCOSIL 500 mg INJECTION: 45/20.1.2/0786

TRYCOSIL 1 g INJECTION: 45/20.1.2/0787

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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