YSP TIDACT® 150mg/ml SOLUTION FOR INJECTION

Ingredient(s):
Each ml contains:
Clindamycin (as Clindamycin Phosphate) 150mg
Benzyl Alcohol (as preservative) 9.45mg

Pharmacodynamic:
Mode of action
Clindamycin is a lincosamide antibiotic with a primarily bacteriostatic action against Gram-positive aerobes and a wide range of anaerobic bacteria. Lincosamides such as clindamycin bind to the 50S subunit of the bacterial ribosome similarly to macrolides such as erythromycin and inhibit the early stages of protein synthesis. The action of clindamycin is predominantly bacteriostatic although high concentrations may be slowly bactericidal against sensitive strains.

Mechanism of resistance
Resistance to clindamycin usually occurs via macrolide-lincosamide-streptogramin B (MLS_B) type of resistance, which may be constitutive or inducible. Clindamycin demonstrates cross-resistance with lincomycin. When tested by in vitro methods, some staphylococcal strains originally resistant to erythromycin rapidly developed resistance to clindamycin. The mechanisms for resistance are the same as for erythromycin, namely methylation of the ribosome binding site, chromosomal mutation of the ribosomal protein and in a few staphylococcal isolates enzymatic inactivation by a plasmid-mediated adenyltransferase.

Breakpoints
The minimum inhibitory concentrations (MIC) breakpoints are as follows:
Eucast
Staphylococci: sensitive ≤ 0.5 resistant > 0.5
Streptococci ABCG and pneumoniae: sensitive ≤ 0.5 resistant > 0.5
Gram positive anaerobes: sensitive ≤ 4 resistant > 4
Gram negative anaerobes: sensitive ≤ 4 resistant > 4

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

Species
- **Susceptible**
  - **Gram-positive aerobes**
    Staphylococcus aureus *
    Staphylococcus epidermidis
    Streptococcus pneumoniae
    Streptococcus pyogenes
    Streptococcus viridans
  - **Anaerobes**
    Bacteriodes fragilis group
    Bacteroides melaninogenicus
    Bifidobacterium spp.
    Clostridium perfringens
    Eubacterium spp.
    Fusobacterium spp.
    Peptococcus spp.
    Peptostreptococcus spp.
    Propionibacterium spp.
    Veillonella spp.
- **Resistant**
  Clostridia spp.
  Enterococci
  Enterobacteriaceae

* Up to 50% of methicillin-susceptible *S. aureus* have been reported to be resistant to clindamycin in some areas. More than 90% of methicillin-resistant *S.aureus* (MRSA) are resistant to clindamycin and it should not be used while awaiting susceptibility test results if there is any suspicion of MRSA.

Pharmacokinetic:
General characteristics of active substance
Following parenteral administration, the biologically inactive clindamycin phosphate is hydrolysed to clindamycin. When the equivalent of 300mg of clindamycin is injected intramuscularly, a mean peak plasma concentration of 6 microgram/ml is achieved within three hours; 600mg gives a peak concentration of 9 microgram/ml. In children, peak concentration may be reached within one hour. When the same doses are infused intravenously, peak concentrations of 7 and 10 micrograms per ml respectively are achieved by the end of infusion.

Clindamycin is widely distributed in body fluids and tissues, including bone, but it does not reach the cerebrospinal fluid in significant concentrations. It diffuses across the placenta into the foetal circulation and appears in breast milk. High concentrations occur in bile. It accumulates in leucocytes and macrophages. Over 90% of clindamycin in the circulation is bound to plasma proteins. The half-life is 2 to 3 hours, although this may be prolonged in pre-term neonates and patients with severe renal impairment.

Clindamycin undergoes metabolism, to the active *N-demethyl* and sulphoxide metabolites and also some inactive metabolites. About 10% of the drug is excreted in the urine as active drug or metabolites and about 4% in the faeces; the remainder is excreted as inactive metabolites. Excretion is slow and takes place over several days. It is not effectively removed from the blood by dialysis.

Indication:
Clindamycin has been shown to be effective in the treatment of the following infections when caused by susceptible anaerobic bacteria; susceptible strains of gram positive aerobic bacteria such as streptococci, staphylococci and pneumococci; and susceptible strains of *Chlamydia trachomatis.*
a) Upper respiratory infections including tonsillitis, pharyngitis, sinusitis, otitis media and scarlet fever.
b) Lower respiratory infection including bronchitis, pneumonia, empyema and lung abscess.
c) Skin and soft tissue infections including acne, furuncles, cellulitis, impetigo, abscesses, and wound infections, specific skin and soft tissue infections caused by susceptible organisms like erysipelas and paranychia (panaritium)
d) Bone and joint infections including osteomyelitis and septic arthritis.
e) Gynecological infections including endometritis, cellulitis, vaginal cuff infection and tubo-ovarian abscess, salpingitis, and pelvic inflammatory disease when given in conjunction with an antibiotic of appropriate gram negative spectrum. In cases of cervicitis due to *Chlamydia trachomatis*, single drug therapy with clindamycin has been shown to be effective in eradicating the organism.
f) Intra-abdominal infections including peritonitis and abdominal abscess when given in conjunction with an antibiotic of appropriate gram negative aerobic spectrum.
g) Septicemia and endocarditis – the effectiveness of clindamycin in the treatment of selected cases of endocarditis has been documented when clindamycin is determined to be bactericidal to the infecting organism by in vitro testing of appropriate achievable serum concentrations.
h) Dental infections such as periodontal abscess and periodontitis.
i) Toxoplasmic encephalitis in patients with AIDS. In patients who are intolerant to conventional treatment, clindamycin in combination with pyrimethamine has been shown to be efficacious.
j) *Pneumocystis jiroveci* (previously classified as *Pneumocystis carinii*) pneumonia in patients with AIDS. In patients who are intolerant to, or do not respond adequately to conventional treatment, clindamycin may be used in combination with primaquine.

Clindamycin phosphate, when used concurrently with an aminoglycoside antibiotic such as gentamicin or tobramycin, has been shown to be effective in preventing peritonitis or intra-abdominal abscess after bowel perforation and bacterial contamination secondary to trauma.

In-vitro susceptibility to clindamycin has been shown for the following organisms; *B.melaninogenicus, B.disiens, B. bivius, Peptostreptococcus spp., G.vaginalis, M.mulieris, M.curtisii and Mycoplasma hominis.*

Dosage and Administration:

As this preparation contains benzyl alcohol, its use should be avoided in children under two years of age.
Not to be used in neonates.

Dosage in Adults
Clindamycin phosphate IM administration should be used undiluted.
Clindamycin phosphate IV administration should be diluted.
Clindamycin phosphate (IM or IV administration):
The usual daily adult dosage of clindamycin phosphate for infections of the intra-abdominal area, female pelvis, and other complicated or serious infections is 2400-2700 mg given in 2, 3, or 4 equal doses. Less complicated infections due to more susceptible microorganisms may respond to lower doses such as 1200-1800 mg/day administered in 3 or 4 equal doses.
Doses of up to 4800 mg daily have been used successfully.
Single IM doses of greater than 600 mg are not recommended.

Dosage in Children (from 2 years of age)
Clindamycin phosphate (IM or IV administration):
20-40 mg/kg/day in 3 or 4 equal doses.
Clindamycin hydrochloride capsules (oral administration) for Children who are able to swallow capsules:
To avoid the possibility of esophageal irritation, clindamycin HCl capsules should be taken with a full glass of water. Clindamycin capsules are not suitable for children who are unable to swallow them whole.
Doses of 8-25 mg/kg/day in 3 or 4 equal doses.

Dosage in Elderly
Pharmacokinetic studies with clindamycin have shown no clinically important differences between young and elderly subjects with normal hepatic function and normal (age-adjusted) renal function after oral or intravenous administration. Therefore, dosage adjustments are not necessary in the elderly with normal hepatic function and normal (age-adjusted) renal function.

Dosage in Renal Impairment
Clindamycin dosage modification is not necessary in patients with renal insufficiency.

Dosage in Hepatic Impairment
Clindamycin dosage modification is not necessary in patients with hepatic insufficiency.

Dosage in Specific Indications
(a) Treatment of Beta-Hemolytic Streptococcal Infections
Refer to the dosage recommendations above (see Dosage and Administration: Dosage in Adults and Dosage in Children (from 2 years of age). Treatment should be continued for at least 10 days.

(b) Inpatient Treatment of Pelvic Inflammatory Disease
Clindamycin phosphate 900 mg (IV) every 8 hours daily plus an antibiotic with an appropriate gram negative aerobic spectrum administered IV, e.g., gentamicin 2.0 mg/kg followed by 1.5 mg/kg every 8 hours daily in patients with normal renal function. Continue (IV) drugs for at least 4 days and at least 48 hours after the patient improves. Then continue oral clindamycin hydrochloride 450-600 mg q6h daily to complete 10-14 days total therapy.

(c) Treatment of Toxoplasmic Encephalitis in Patients with AIDS

Clindamycin phosphate IV or clindamycin hydrochloride orally 600-1200 mg every 6 hours for 2 weeks followed by 300-600 mg orally every 6 hours. The usual total duration of therapy is 8 to 10 weeks. The dose of pyrimethamine is 25 to 75 mg orally each day for 8 to 10 weeks. Folinic acid 10 to 20 mg/day should be given with higher doses of pyrimethamine.

(d) Treatment of Pneumocystis jiroveci (previously classified as Pneumocystis carinii) Pneumonia in Patients with AIDS
Clindamycin phosphate IV 600 to 900 mg every 6 hours or 900 mg IV every 8 hours or clindamycin hydrochloride 300 to 450 mg orally every 6 hours for 21 days and Primaquine 15 to 30 mg dose orally once daily for 21 days.

Dilution and IV infusion rates
Diluent:
5% Dextrose Solution, 10% Dextrose Solution, 0.9% Sodium Chloride Solution, 5% Dextrose in 0.45% Sodium Chloride Solution and 5% Dextrose in 0.9% Sodium Chloride Solution.

The concentration of clindamycin in diluents for infusion should not exceed 18mg/ml and infusion rates should not exceed 30mg per minute. The usual infusion rates are as follows:

Dose	Diluent	Time
300mg	50ml	10min
600mg	50ml	20min
900mg	50-100ml	30min
1200mg	100ml	40min

Administration of more than 1200mg in a single 1-hour infusion is not recommended.

Incompatibilities: When combined with clindamycin phosphate in an infusion solution, ampicillin, phenytoin sodium, barbiturates, aminophyllin, calcium gluconate, magnesium sulfate, ceftriaxone sodium, and ciprofloxacin are each physically incompatible with clindamycin phosphate.

Mode of Administration
IM or IV.

Contraindication(s):
Clindamycin is contraindicated in patients previously found to be sensitive to clindamycin or lincomycin or to any component of the formulation.

Precaution(s) / Warning(s):

- As this preparation contains benzyl alcohol, its use should be avoided in children under two years of age. Not to be used in neonates.
- Clindamycin therapy has been associated with severe colitis which may end fatally.
- It should be reserved for serious infections where less toxic antimicrobial agents are inappropriate.
- It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections.
- Its use in newborns is contraindicated.

1. Clindamycin should only be used in the treatment of serious infections. In considering the use of the product, the practitioner should bear in mind the type of infection and the potential hazard of the diarrhoea which may develop, since cases of colitis have been reported during, or even two or three weeks following, the administration of clindamycin.
2. *Clostridium difficile* associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including clindamycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.
3. *C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.
4. Caution should be used when prescribing clindamycin to individuals with a history of gastro-intestinal disease, especially colitis.
5. Periodic liver and kidney function and haematology tests should be carried out during prolonged therapy.
6. Prolonged administration of clindamycin, as with any anti-infective, may result in super-infection due to organisms resistant to clindamycin. The use of clindamycin may result in the overgrowth of non-susceptible organisms particularly yeasts.
7. Care should be observed in the use of clindamycin in atopic individuals, particularly those with asthma.
8. Since clindamycin does not diffuse adequately into cerebrospinal fluid, the drug should not be used in the treatment of meningitis.
9. Antibiotics can reduce the efficacy of the combined oral contraceptive pill. Additional contraceptive precautions should be taken during treatment and for up to seven days after stopping treatment.
10. Clindamycin is potentially nephrotoxic. Acute kidney injury including acute renal failure has been reported. Therefore, monitoring of renal function should be considered during therapy of patients with pre-existing renal dysfunction or taking concomitant nephrotoxic drugs and monitoring of renal function should be performed if therapy is prolonged.

Interaction with Other Medicaments:
1. *Neuromuscular blocking agents*: Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. It should be used with caution, therefore, in patients receiving such agents.
2. *Erythromycin*: Antagonism has been demonstrated between clindamycin and erythromycin in vitro. Because of possible clinical significance, the two drugs should not be administered concurrently.
3. *Vitamin K antagonists*: Increased coagulation tests (PT/INR) and/or bleeding have been reported in patients treated with clindamycin in combination with a vitamin K antagonist (e.g. warfarin, acenocoumarol and fluindione). Coagulation tests, therefore, should be frequently monitored in patients treated with vitamin K antagonists.

Pregnancy and Lactation:
1. Safety for use in pregnancy has not been established. Animal studies do not indicate reproductive toxicity.
2. *Lactation*: Clindamycin is excreted in human milk. Caution should be exercised when clindamycin is administered to a nursing mother. It is unlikely that a nursing infant can absorb a significant amount of clindamycin from its gastro-intestinal tract.

Side Effect(s):
Effects on ability to drive and use machines
The effect of clindamycin on the ability to drive or operate machinery has not been systematically evaluated.

Undesirable effects
Gastro-intestinal tract disorders: Oesophageal ulcers have been reported as serious adverse events during postmarketing surveillance, and oesophagitis with oral preparations, nausea, vomiting, abdominal pain and diarrhoea.

Blood and lymphatic system disorders: Transient neutropenia (leucopenia), eosinophilia, agranulocytosis and thrombocytopenia have been reported. No direct aetiologic relationship to concurrent clindamycin therapy could be made in any of the foregoing.

Immune system disorders: a few cases of anaphylactoid reactions have been reported.

Skin and subcutaneous tissue disorders: Maculopapular rash and urticaria have been observed during drug therapy. Generalised mild to moderate morbilliform-like skin rashes are the most frequently reported reactions. Rare instances of erythema multiforme some resembling Stevens-Johnson syndrome, have been associated with clindamycin. Pruritus, vaginitis and rare instances of exfoliative and vesiculobullous dermatitis have been reported. Serious cutaneous adverse reaction (SCAR) and rare cases of toxic epidermal necrolysis have been reported during postmarketing surveillance.

Hepatobiliary disorders: Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy.

Cardiac disorders: Rare instances of cardiopulmonary arrest and hypotension have been reported following too rapid intravenous administration.

Nervous system disorders: Frequent cases of dysgeusia have been observed upon systemic administration of clindamycin using injectables (IM or IV), capsules or oral granulate solutions, which include a few (non-frequent) serious adverse events.

General disorders and administration site conditions: Local irritation, pain, abscess formation have been observed in conjunction with IM injection. These reactions can be minimised by deep IM injection and avoiding the use of an indwelling catheter.

Renal and urinary disorders: Acute kidney injury (frequency not known)

Thrombophlebitis has been reported with IV injection.

Symptoms and Treatment for Overdosage, and Antidote(s):
In cases of overdosage no specific treatment is indicated.

The serum biological half-life of clindamycin is 2.4 hours. Clindamycin cannot readily be removed from the blood by dialysis or peritoneal dialysis.

If an allergic adverse reaction occurs, therapy should be with the usual emergency treatments, including corticosteroids, adrenaline and antihistamines.

Shelf-Life:
3 years from the date of manufacture.
For solution diluted with 5% Dextrose Solution, 10% Dextrose Solution, 0.9% Sodium Chloride Solution, 5% Dextrose in 0.45% Sodium Chloride Solution and 5% Dextrose in 0.9% Sodium Chloride Solution, chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.

Storage Condition(s):
Store under refrigeration between 2°C and 8°C.
Store at 25°C after dilution for IV infusion.
Protect from light and moisture.

Product Description:
A clear and colorless to slightly yellowish solution.
After dilution: Clear and colorless solution.

Dosage Forms and Packaging Available:
2ml x 10 vials, 2ml x 50 vials

Y. S. P.®
Manufacturer and Product Registration Holder:
Y.S.P. INDUSTRIES (M) SDN. BHD. (199001001034)
Lot 3, 5, 7, 12 & 14, Jalan P/7, Section 13,
Kawasan Perindustrian Bandar Baru Bangi,
43000 Kajang, Selangor, Malaysia.
Ordering Line: 1 800 88 3027
Product Info: 1 800 88 3679

Date of revision: 22 Nov 2024