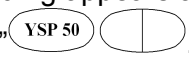
Summary of Product Characteristics

1. **Name of the finished pharmaceutical product:**
   Clarimycin Film Coated Tablet 500mg

2. **Qualitative and quantitative composition:**
   2.1 Qualitative Declaration:
   Clarithromycin contains not less than 96.0% and not more than 102.0% of $C_{38}H_{69}NO_{13}$, calculated on the anhydrous basis.

   2.2 Quantitative Declaration:
   Each tablet contains:
   Clarithromycin …….500mg

3. **Pharmaceutical form:**
   Clarimycin Film Coated Tablet 500mg appears as a light yellow rounded rectangular tablet, one side impressed with "YSP 50" 

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4. **Clinical Particulars:**
   4.1.Therapeutic indication:
   Treatment of infections caused by pathogens sensitive to Clarithromycin. Infections of nose-pharynx tract (tonsillitis, pharyngitis) and of paranasal sinuses. Infections of lower respiratory tract: bronchitis and bacterial pneumonia. Skin infections and soft tissue infections of mild to moderate severity. Triple therapy eradication of *H.pylori* in patients with duodenal ulcers in adults.
   This 500mg tablet is not suitable for doses below 500mg
   Delivery conditions: This medicinal product is subject to medical prescription (POM)

   4.2.Posology and method of administration:
   Patients with respiratory tract/skin and soft tissue infections.
   Adults: The usual dose is 250 mg twice daily although this may be increased to 500mg twice daily in severe infections. The usual duration of treatment is 6 to 14 days.
   Children older than 12 years: As for adults.
   Children younger than 12 years:
   Use of Clarithromycin 500mg Tablets are not recommended for children younger than 12 years. Clinical trials have been conducted using clarithromycin paediatric suspension in children 6 months to 12 years of age. Therefore, children under 12 years of age should use clarithromycin paediatric suspension (granules for oral suspension).
   Clarithromycin may be given without regard to meals as food does not affect the extent of bioavailability.

   Renal impairment:
   In patients with renal impairment with creatinine clearance less than 30 mL/min, the dosage of clarithromycin should be reduced by one-half, i.e. 250 mg once daily, or 250 mg twice daily in more severe infections. Treatment should not be continued beyond 14 days in these patients.

   Method of administration: Oral

4.3.Contraindication:

Patients hypersensitive to macrolides. Clarithromycin is contraindicated in patients receiving terfenadine therapy who have pre-existing cardiac abnormalities (arrhythmia, bradycardia, QT interval prolongation, ischemic heart disease, congestive heart failure, etc) or electrolyte disturbances.

Concomitant administration of clarithromycin and any of the following drugs is contraindicated: astemizole, cisapride, domperidone, pimozide and terfenadine as this may result in QT prolongation and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes.

Clarithromycin should not be used concomitantly with HMGCoA reductase inhibitors (statins) that are extensively metabolized by CYP3A4, (lovastatin and simvastatin), due to the increased risk of myopathy, including rhabdomyolysis.

Clarithromycin should not be given to patients with electrolyte disturbances (hypokalaemia or hypomagnesaemia, due to the risk of prolongation of QT interval).

4.4.Special warnings and special precautions for use:

Use of any antimicrobial therapy, such as clarithromycin, to treat *H. pylori* infection may select for drug-resistant organisms.

The physician should not prescribe clarithromycin to pregnant women without carefully weighing the benefits against risk; particularly during the first three months of pregnancy.

Clarithromycin is principally metabolised by the liver. Therefore, caution should be exercised in administering this antibiotic to patients with impaired hepatic function.

Caution should also be exercised when administering clarithromycin to patients with moderate to severe renal impairment.

Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been reported with clarithromycin. This hepatic dysfunction may be severe and is usually reversible. Cases of fatal hepatic failure have been reported. Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products. Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop, such as anorexia, jaundice, dark urine, pruritus, or tender abdomen.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides, and may range in severity from mild to life-threatening. *Clostridium difficile*- associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents including clarithromycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, which may lead to overgrowth of *C. difficile.* 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. Therefore, discontinuation of clarithromycin therapy should be considered regardless of the indication. Microbial testing should be performed and adequate treatment initiated. Drugs inhibiting peristalsis should be avoided.

There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients. Concomitant administration of clarithromycin and colchicine is contraindicated.

Caution is advised regarding concomitant administration of clarithromycin and triazolobenzodiazepines, such as triazolam and intravenous or oromucosal and midazolam.

Cardiovascular Events

Prolongation of the QT interval, reflecting effects on cardiac repolarisation imparting a risk of developing cardiac arrhythmia and *torsades de pointes*, have been seen in patients treated with macrolides including clarithromycin. Due to increased risk of QT prolongation and ventricular arrhythmias (including *torsades de pointes*), the use of clarithromycin is contraindicated: in patients taking any of astemizole, cisapride, domperidone, pimozide and terfenadine; in patients who have hypokalaemia; and in patients with a history of QT prolongation or ventricular cardiac arrhythmia.

Furthermore, clarithromycin should be used with caution in the following:

• Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia;

• Patients with hypomagnesaemia;

• Patients concomitantly taking other medicinal products associated with QT prolongation other than those which are contraindicated

Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short-term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including clarithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing clarithromycin.

Pneumonia: In view of the emerging resistance of *Streptococcus pneumonia* to macrolides, it is important that sensitivity testing be performed when prescribing clarithromycin for community-acquired pneumonia. In hospital-acquired pneumonia, clarithromycin should be used in combination with additional appropriate antibiotics.

Skin and soft tissue infections of mild to moderate severity: These infections are most often caused by *Staphylococcus aureus* and *Streptococcus pyogenes*, both of which may be resistant to macrolides. Therefore, it is important that sensitivity testing be performed. In cases where *beta*–lactam antibiotics cannot be used (e.g. allergy), other antibiotics, such as clindamycin, may be the drug of first choice. Currently, macrolides are only considered to play a role in some skin and soft tissue infections, such as those caused by *Corynebacterium minutissimum*, acne vulgaris, and erysipelas and in situations where penicillin treatment cannot be used.

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCAR) (e.g. Acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome, toxic epidermal necrolysis and drug rash with eosinophilia and systemic symptoms (DRESS)), clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

Clarithromycin should be used with caution when administered concurrently with medications that induce the cytochrome CYP3A4 enzyme.

HMG-CoA Reductase Inhibitors (statins): Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated. Caution should be exercised when prescribing clarithromycin with other statins. Rhabdomyolysis has been reported in patients taking clarithromycin and statins. Patients should be monitored for signs and symptoms of myopathy.

In situations where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin) can be considered.

Oral hypoglycaemic agents/Insulin: The concomitant use of clarithromycin and oral hypoglycaemic agents (such as sulphonylurias) and/or insulin can result in significant hypoglycaemia. Careful monitoring of glucose is recommended.

Oral anticoagulants: There is a risk of serious haemorrhage and significant elevations in International Normalized Ratio (INR) and prothrombin time when clarithromycin is co-administered with warfarin. INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants concurrently.

Long-term use may, as with other antibiotics, result in colonisation with increased numbers of non-susceptible bacteria and fungi. If superinfections occur, appropriate therapy should be instituted.

Attention should also be paid to the possibility of cross resistance between clarithromycin and other macrolide drugs, as well as lincomycin and clindamycin.

4.5. Interaction with other FPPs and other forms of interaction:

Results of clinical studies indicate that there was a modest but statistically significant increase (p 0.05) of circulating theophylline or carbamazepine levels when either of these drugs are administered concomitantly with Clarithromycin. As with other macrolide antibiotics, the use of Clarithromycin in patients concurrently taking drugs metabolized by the cytochrome P-450 system (eg. digoxin, warfarin) may be associated with elevations in serum levels of these other drugs.

Macrolides have been reported to alter the metabolism of terfenadine resulting in increased levels of terfenadine which has occasionally been associated with cardiac arrhythmias. In 1 study in 14 healthy volunteers, the concomitant administration of Clarithromycin and terfenadine resulted in 2 to 3 fold increases in the serum level of the acid metabolite of terfenadine and in prolongation of the QT-interval which did not lead to any clinically detectable effect.

4.6. Pregnancy and lactation:

1. Use in pregnancy: Adequate and well-controlled studies in humans have not been done.
2. Lactation: Clarithromycin and its active metabolite are distributed into breast milk.

4.7. Effects on ability to drive and use machines:

No information available.

4.8. Undesirable effects:

a. Summary of the safety profile

The most frequent and common adverse reactions related to clarithromycin therapy for both adult and paediatric populations are abdominal pain, diarrhoea, nausea, vomiting and taste perversion. These adverse reactions are usually mild in intensity and are consistent with the known safety profile of macrolide antibiotics.

There was no significant difference in the incidence of these gastrointestinal adverse reactions during clinical trials between the patient population with or without pre-existing mycobacterial infections.

b. Tabular summary of adverse reactions

The following table displays adverse reactions reported in clinical trials and from post-marketing experience with clarithromycin immediate-release tablets, granules for oral suspension, powder for solution for injection, extended-release tablets and modified-release tablets.

The reactions considered at least possibly related to clarithromycin are displayed by system organ class and frequency using the following convention: very common (≥1/10), common (≥ 1/100 to < 1/10), uncommon (≥1/1,000 to < 1/100) and not known (adverse reactions from post-marketing experience; cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness when the seriousness could be assessed.

System organ class	Very common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥ 1/1, 000 to <1/100	Not Known* (cannot be estimated from the available data)
Infections and Infestations			Cellulitis[1], candidiasis, gastroenteritis[2], infection[3], vaginal infection	Pseudomembranous colitis, erysipelas,
Blood and lymphatic system			Leukopenia, neutropenia[4], thrombocythaemia[3], eosinophilia[4]	Agranulocytosis, thrombocytopenia
Immune system disorders			Anaphylactoid reaction[1], hypersensitivity	Anaphylactic reaction. angioedema
Metabolism and nutrition disorders			Anorexia, decreased appetite	
Psychiatric disorders		Insomnia	Anxiety, nervousness[3]	Psychotic disorder, confusional state[5], depersonalisation, depression, disorientation, hallucinations, abnormal dreams, mania
Nervous system disorders		Dysgeusia, headache	Loss of consciousness[1], dyskinesia[1], dizziness, somnolence[5], tremor	Convulsions, ageusia, parosmia, anosmia,
Ear and labyrinth			Vertigo, hearing impaired, tinnitus	Deafness
Cardiac disorders			Cardiac arrest[1], atrial fibrillation[1], electrocardiogram QT prolonged, extrasystoles[1], palpitations	Torsades de pointes, ventricular tachycardia , ventricular fibrillation
Vascular disorder		Vasodilation[1]		Haemorrhage
Respiratory, thoracic and mediastinal disorder			Asthma[1], epistaxis[2], Pulmonary embolism[1].	
Gastrointestinal disorder		Diarrhoea, vomiting, dyspepsia, nausea, abdominal pain	Oesophagitis[1], gastrooesophageal reflux disease[2], gastritis, proctalgia[2], stomatitis, glossitis, abdominal distension[4], constipation, dry	Pancreatitis acute , tongue discolouration, tooth discolouration

Hepatobiliary disorders		Liver function test abnormal	Cholestasis[4], hepatitis[4], alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased[4]	Hepatic failure, jaundice hepatocellular
Skin and subcutaneous tissue disorders		Rash, hyperhidrosis	Dermatitis bullous[1], pruritus, urticaria, rash maculo-papular[3]	Severe cutaneous adverse reactions (SCAR) (e.g. Acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms
Musculoskeletal and connective tissues			Muscle spasms[3], musculoskeletal stiffness[1], myalgia[2]	Rhabdomyolysis [2, 6], myopathy
Renal and urinary disorders			Blood creatinine Increased[1] , blood urea increased[1]	Renal failure, nephritis interstitial
General disorders and administration site conditions	Injection site phlebitis[1]	Injection site pain[1], injection site inflammation[1]	Malaise[4], pyrexia[3], asthenia, chest pain[4] , chills[4], fatigue[4]	
Investigations			Albumin globulin ratio abnormal[1], blood alkaline phosphatase increased[4], blood lactate dehydrogenase increased[4]	International normalised ratio, increased, prothrombin time prolonged, urine colour abnormal

[1] ADRs reported only for the Powder for Concentrate for Solution for Infusion formulation

[2]ADRs reported only for the Extended-Release Tablets formulation

[3] ADRs reported only for the Granules for Oral Suspension formulation

[4] ADRs reported only for the Immediate-Release Tablets formulation

[5,6] See section c below)

** Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Patient exposure is estimated to be greater than 1 billion patient treatment days for clarithromycin.*

c. Description of selected adverse reactions

Injection site phlebitis, injection site pain, and injection site inflammation are specific to the clarithromycin intravenous formulation.

In some of the reports of rhabdomyolysis, clarithromycin was administered concomitantly with statins, fibrates, colchicine or allopurinol.

There have been post-marketing reports of drug interactions and central nervous system (CNS) effects (e.g. somnolence and confusion) with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested.

There have been rare reports of clarithromycin ER tablets in the stool, many of which have occurred in patients with anatomic (including ileostomy or colostomy) or functional gastrointestinal disorders with shortened GI transit times. In several reports, tablet residues have occurred in the context of diarrhoea. It is recommended that patients who experience tablet residue in the stool and no improvement in their condition should be switched to a different clarithromycin formulation (e.g. suspension) or another antibiotic.

Special population: Adverse Reactions in Immunocompromised Patients (see section e below).

d. Paediatric population

Clinical trials have been conducted using clarithromycin paediatric suspension in children 6 months to 12 years of age. Therefore, children under 12 years of age should use clarithromycin paediatric suspension.

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

e. Other special populations

Immunocompromised patients

In AIDS and other immunocompromised patients treated with the higher doses of clarithromycin over long periods of time for mycobacterial infections, it was often difficult to distinguish adverse events possibly associated with clarithromycin administration from underlying signs of Human Immunodeficiency Virus (HIV) disease or intercurrent illness.

In adult patients, the most frequently reported adverse reactions by patients treated with total daily doses of 1000 mg and 2000mg of clarithromycin were: nausea, vomiting, taste perversion, abdominal pain, diarrhoea, rash, flatulence, headache, constipation, hearing disturbance, Serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum Glutamic Pyruvate Transaminase (SGPT) elevations. Additional low-frequency events included dyspnoea, insomnia and dry mouth. The incidences were comparable for patients treated with 1000mg and 2000mg, but were generally about 3 to 4 times as frequent for those patients who received total daily doses of 4000mg of clarithromycin.

In these immunocompromised patients, evaluations of laboratory values were made by analysing those values outside the seriously abnormal level (i.e. the extreme high or low limit) for the specified test. On the basis of these criteria, about 2% to 3% of those patients who received 1000mg or 2000mg of clarithromycin daily had seriously abnormal elevated levels of SGOT and SGPT, and abnormally low white blood cell and platelet counts. A lower percentage of patients in these two dosage groups also had elevated Blood Urea Nitrogen levels. Slightly higher incidences of abnormal values were noted for patients who received 4000mg daily for all parameters except White Blood Cell.

4.9.Overdose:

Reports indicate that the ingestion of large amounts of Clarithromycin can be expected to produce gastrointestinal symptoms. Allergic reactions accompanying overdosage should be treated by prompt elimination of unabsorbed drug and supportive measures. As with other macrolides, Clarithromycin plasma levels are not expected to be appreciably affected by hemodialysis or peritoneal dialysis.

5. Pharmacological properties:

5.1.Pharmacodynamic properties:

Clarithromycin exerts its antibacterial activity by inhibiting the synthesis of proteins, by means of a link with the 50S sub-unit of the cellular ribosome. Clarithromycin has demonstrated excellent *in vitro* activity against both standard strains of bacteria and

clinical isolates. It is highly potent against a wide variety of aerobic and anaerobic gram-positive and gram-negative organisms.

5.2.Pharmacokinetic properties:

1. **Absorption:** Well absorbed from the gastrointestinal tract; stable in gastric acid; food delays the rate, but not the extent, of absorption; bioavailability is approximately 55% in healthy volunteers.
2. **Distribution:** Widely distributed into tissues and fluids; high concentrations found in nasal mucosa, tonsils, and lungs; concentrations in tissues are higher than those in serum because of high intracellular concentrations; readily enters leucocytes and macrophages. Volume of distribution: 243-266 liters.
3. **Protein binding**: High (65 – 75%).
4. **Biotransformation**: Hepatically metabolized via three main pathways, demethylation, hydroxylation, and hydrolysis, to eight metabolites. One metabolite, 14-hydroxyclarithromycin, has *in vitro* antimicrobial activity comparable to that of Clarithromycin and may act synergistically with Clarithromycin against *Haemophilus influenzae*. Saturation of metabolism involves the demethylation and hydroxylation pathways, and accounts for an increase in serum half-life.
5. **Half life**:
   Clarithromycin:
   250mg every 12 hours – 3 to 4 hours
   500mg every 12 hours – 5 to 7 hours
   14-hydroxyclarithromycin:
   250mg every 12 hours – 5 to 6 hours
   500mg every 12 hours – approximately 7 hours
   Normal renal function:
   Clarithromycin : approximately 22 hours
   14-Hydroxyclarithromycin : approximately 47 hours
6. **Time to peak concentration**: 2 to 3 hours.
7. **Peak serum concentration**:
   Clarithromycin (at steady state)
   250mg (tablet) every 12 hours – approximately 1mcg/ml
   500mg (tablet) every 12 hours – 2 to 3 mcg/ml
   14-Hydroxyclarithromycin (at steady state)
   250mg (tablet) every 12 hours – approximately 0.6 mcg/ml
   500mg (tablet) every 12 hours – up to 1mcg/ml
8. **Elimination**:
   Renal – Approximately 20% and 30% of the dose of 250mg and 500mg tablets, respectively, given twice a day, is excreted in the urine as unchanged drug. 14-Hydroxyclarithromycin accounts for 10% and 15% of the dose excreted in the urine after doses of 250mg and 500mg, respectively, given twice a day.
   Fecal – Approximately 4% of a 250mg dose is excreted in the feces.

5.3.Preclinical safety data:

No information available.

6. Pharmaceutical particulars:

6.1.List of excipients:

1. Microcrystalline Cellulose
2. Sodium Starch Glycolate
3. Sorbitan Trioleate
4. Sorbic Acid
5. Carboxymethylcellulose Sodium
9. Povidone
10. Polyethylene Glycol
11. Colloidal Silicon Dioxide
12. Pregelatinized Starch
13. Isopropyl Alcohol

6. Magnesium Stearate
7. Talc
8. Stearic Acid
14. Croscarmellose Sodium
15. Opadry II Yellow
16. Purified Water

6.2. Incompatibilities:
No information available.

6.3. Shelf life:
3 years from the date of manufacture.

6.4. Special precautions for storage:
Store at temperature below 30°C. Protect from light and moisture.

6.5. Nature and contents of container:
Blister Packing of 10's x 10 and 10's x 2.

6.6. Instructions for use and handling <and disposal>:
None has been mentioned.

7. Marketing authorization holder:

Name : Y. S. P. INDUSTRIES (M) SDN. BHD.

Address : Lot 3, 5 & 7, Jalan P/7, Section 13,
Kawasan Perindustrian Bandar Baru Bangi,
43000 Kajang, Selangor Darul Ehsan,
Malaysia.

8. Number(s) in the national register of finished pharmaceutical products:
TAN 22 HM 0191

9. Date of first authorization / renewal of the authorization

04th May, 2022

10. Date of revision of the text