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:**

   Tablet

4- Clinical Particulars

4.1 Therapeutic indications:

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, bacterial pneumonia and atypical pneumonia. Skin infections: impetigo, erysipelas, folliculitis, furunculosis and septic wounds.

4.2 Posology and method of administration:

Clarithromycin recommended dosage in adults is one 250mg tab every 12 hours. In cases of severe infections, dosage can be increased up to 500mg every 12 hours.

Administration must be continued, according to severity of infection, up to 6-14 days.

In patients with renal impairment with creatinine clearance <30mL/min, the dosage should be reduced by half. Dosage should not be continued beyond 14 days in these patients.

To be taken orally.

4.3 Contraindications:

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

4.4 Special warning and precautions for use:

a) It has been demonstrated that clarithromycin can interfere with carbamazepine plasma levels which can significantly increase. Patients administered with such a combination must be clinically monitored and, if necessary, relevant posology modifications must be made. Clarithromycin can cause an increase of theophylline plasma concentrations, slight enough to not justify a modification of theophylline usual posology.

b) Clarithromycin is principally excreted by the liver. Therefore, caution should be exercised in administering the antibiotic to patients with impaired hepatic function. Caution should also be exercised when administering clarithromycin to patients with moderate to severe renal failure. Attention should also be paid to the possibility of cross-resistance between clarithromycin and other macrolide drugs, as well as lincomycin and clindamycin.

c) In the event of severe acute hypersensitivity reactions, such as anaphy-laxis, severe cutaneous adverse reactions (SCARs) [e.g. Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP)], this

product should be discontinued immediately and appropriate treatment should be urgently initiated.

4.5 Interaction with other medicinal products and other forms of Interactions:

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:

Use in pregnancy

- Adequate and well-controlled studies in humans have not been done.

Lactation

- Clarithromycin and its active metabolite are distributed into breast milk.

4.7 Effects on ability to drive and use machine:

No information available.

4.8 Undesirable effects:

a) The majority of adverse events reported were of the gastrointestinal system, eg. diarrhea, vomiting, abdominal pain, dyspepsia and nausea. Other adverse events included headache, altered taste and transient elevations of liver enzymes. Allergic reactions ranging from urticaria and mild skin eruptions to anaphylaxis have occurred with orally administered clarithromycin. There have been reports with oral clarithromycin of transient CNS side effects including anxiety, dizziness, insomnia, hallucinations, bad dreams and confusion; however, a cause and effect relationship has not been established.

b) Using macrolides, transient increases of SGOT-SGPT are possible, normally reversible after therapy withdrawal. While during clinical studies with clarithromycin, more severe problems relevant to the liver have not been experienced, it should be taken into account that with antibiotics of this family, episodes of cholestatic hepatitis can exceptionally happen.

c) Like with other antibiotics, during therapy with clarithromycin, superinfections by resistant bacteria or fungi can rarely arise, needing administration withdrawal and adoption of suitable therapies.

d) Skin and Subcutaneous Tissue Disorders

Frequency not known: severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP).

4.9 Overdose and special antidotes:

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:

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.

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.

Protein binding

High (65-75%).

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.

Half-life

a) Clarithromycin:

250mg every 12 hours – 3 to 4 hours.

500mg every 12 hours – 5 to 7 hours.

b) 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.

Time to peak concentration

2 to 3 hours.

Peak serum concentration

a) Clarithromycin (at steady state)

250mg (tablet) every 12 hours – approximately 1mcg/mL

500mg (tablet) every 12 hours – 2 to 3 mcg/mL

b) 14-Hydroxyclarithromycin (at steady state)

250mg (tablet) every 12 hours – approximately 0.6 mcg/mL

500mg (tablet) every 12 hours – up to 1mcg/mL

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:

a) Microcrystalline Cellulose
b) Sodium Starch Glycolate
c) Sorbitan Trioleate
d) Sorbic Acid
e) Carboxymethylcellulose Sodium
f) Magnesium Stearate
g) Talc
h) Stearic Acid
i) Povidone
j) Polyethylene Glycol
k) Colloidal Silicon Dioxide
l) Pregelatinized Starch
m) Isopropyl Alcohol
n) Croscarmellose Sodium
o) Opadry II Yellow
p) Purified Water

6.2 Incompatibilities:

No information available.

6.3 Shelf life:

Blister Pack: 3 years from the date of manufacturing.

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 pack of 10's x 10

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:

Y.S.P. / MAL / 008

07013/08066/REN/2021

9. Date of ~~first~~ authorization / renewal of the authorization:

05 October 2017

Jan 4, 2022

10. Date of revision of the text: 1

4 October 2020