SUMMARY OF PRODUCTS CHARACTERISTICS (SMPC)

1. Name of the Finished Pharmaceutical Product

1.1 Name of the medicinal product

Asrithro (Clarithromycin Tablets BP 500 mg)

1.2 Strength

Each film coated tablets contains:

Clarithromycin BP .....500 mg

1.3 Pharmaceutical form

Tablet

2. Qualitative and quantitative composition

Sr. No.	Ingredient
1	Clarithromycin
2	Microcrystalline cellulose
3	Pregelatinized Starch
4	Sodium starch glycollate
5	Croscarmellose Sodium
6	Purified Talc
7	Silicon dioxide
8	Sodium lauryl Sulphate
9	Magnesium stearate
10	Ready to coat (Tartrazine Yellow)
11	Isopropyl Alcohol
12	Dichloromethane

3. Pharmaceutical form

Dosage Form: Tablet

Physical Characteristics: Light yellow to yellow, flim coated, biconvex oval tablet having breakline on one side and other side plain

4. Clinical particulars

4.1 Therapeutic indications

Clarithromycin tablet is indicated in adults and adolescents 12 years and older for the treatment of the following infections:

- Actute bacterial exacerbation of chronic bronchitis.
- Mild to modrate community acquired pneumonia.
- Acute bacterial sinusitis
- Bacterial pharyngitis.
- Skin infections and soft tissue infections such as folliculitis , cellulitis and erysipelas

4.2 Posology

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. (Adult only formulation)

Children older than 12 years: As for adults.

Children younger than 12 years: Use of clarithromycin tablets are not recommended for children younger than 12 years.

Eradication of H. pylori in patients with duodenal ulcers (Adults)

The usual duration of treatment is 6 to 14 days.

Triple Therapy:

Clarithromycin 500mg twice daily and lansoprazole 30mg twice daily should be given with amoxicillin 1000mg twice daily.

Triple Therapy:

Clarithromycin 500mg twice daily and lansoprazole 30mg twice daily should be given with metronidazole 400mg twice daily.

Triple Therapy:

Clarithromycin 500mg twice daily and omeprazole 40mg daily should be given with amoxicillin 1000mg twice daily or metronidazole 400mg twice daily.

Triple Therapy:

Clarithromycin 500mg twice daily should be given with amoxicillin 1000mg twice daily and omeprazole 20mg daily.

Dual Therapy:

The usual dose of clarithromycin is 500 mg three times daily for 14 days. Clarithromycin should be administered with oral omeprazole 40 mg once daily.

Elderly

As for adults.

Renal impairment

Dosage adjustments are not usually required except in patients with severe renal impairment (creatinine clearance < 30 ml/min). If adjustment is necessary, the total daily dosage should be reduced by half, e.g. 250 mg once daily or 250 mg twice daily in more severe infections. Treatment should not be continued beyond 14 days in these patients. Clarithromycin may be given without regard to meals as food does not affect the extent of bioavailability.

4.3 Method of administration:

Oral route

4.4 Contraindications

Clarithromycin is contraindicated in patients with known hypersensitivity to clarithromycin, to any other macrolide antibiotic drug, or to any of the other ingredients in the tablets. In the case of Clarithromycin 500 mg Film coated Tablets, as the dose cannot be reduced from 500mg daily, Clarithromycin 500 mg film coated Tablets are contraindicated in patients with creatinine clearance less than 30 mL/min. All other formulations may be used in this patient population. Concomitant administration of clarithromycin and ergotamine or dihydroergotamine is contraindicated, as this may result in ergot toxicity.

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

Clarithromycin should not be given to patients with history of QT prolongation or ventricular cardiac arrhythmia, Clarithromycin should not be

used concomitantly with HMGCoA reductase inhibitors (statins) that are extensively metabolized by CYP3A4 (lovastatin or simvastatin), due to increased risk of myopathy, including rhabdomyolysis

As with other strong CYP3A4 inhibitors, Clarithromycin should not be used in patients taking colchicine..Clarithromycin should not be given to patients with hypokalemia (risk of prolongation of QT time).Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment.

4.5 Special warnings and precautions for use

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

Caution is advised regarding concomitant administration of clarithromycin and triazolobenzodiazepines, such as triazolam, and midazolam ototoxic drugs, especially with aminoglycosides, medication that induce the cytochrome CYP3A4 enzyme ,oral hypoglycemic agents such as sulphonylureas and/or insulin and warfarin

4.6 Interaction with other medicinal products and other forms of interaction

Use of the following drugs is strictly contraindicated due to the potential for severe drug interaction effects:

Cisapride, pimozide, astemizole and terfenadine

Elevated cisapride levels have been reported in patients receiving clarithromycin and cisapride concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsades de pointes. Similar effects have been observed in patients taking clarithromycin and pimozide concomitantly.

Macrolides have been reported to alter the metabolism of terfenadine resulting in increased levels of terfenadine which has occasionally been associated with cardiac arrhythmias, such as QT prolongation, ventricular tachycardia, ventricular fibrillation and torsades de pointes.

Ergotamine/dihydroergotamine

Coadministration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm, and

ischemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin and these medicinal products is contraindicated.

HMGCoA Reductase Inhibitors (statins)

Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated as these statins are extensively metabolized by CYP3A4 and concomitant treatment with clarithromycin increases their plasma concentration, which increases the risk of myopathy, including rhabdomyolysis. If treatment with clarithromycin cannot be avoided, therapy with lovastatin or simvastatin must be suspended during the course of treatment. Caution should be exercised when prescribing clarithromycin with statins. 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. Patients should be monitored for signs and symptoms of myopathy.

Effects of Other Medicinal Products on Clarithromycin

Drugs that are inducers of CYP3A (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, St John's wort) may induce the metabolism of clarithromycin. This may result in sub therapeutic levels of clarithromycin leading to reduced efficacy. Furthermore, it might be necessary to monitor the plasma levels of the CYP3A inducer, which could be increased owing to the inhibition of CYP3A by clarithromycin Concomitant administration of rifabutin and clarithromycin resulted in an increase in rifabutin, and decrease in clarithromycin serum levels together with an increased risk of uveitis.

Drugs are known or suspected to affect circulating concentrations of clarithromycin; clarithromycin dosage adjustment or consideration of alternative treatments may be required.

Efavirenz, nevirapine, rifampicin, rifabutin and rifapentine

Strong inducers of the cytochrome P450 metabolism system such as efavirenz, nevirapine, rifampicin, rifabutin, and rifapentine may accelerate the metabolism of clarithromycin and thus lower the plasma levels of clarithromycin, while increasing those of 14-OHclarithromycin, a metabolite

that is also microbiologically active. Since the microbiological activities of clarithromycin and 14-OHclarithromycin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of clarithromycin and enzyme inducers.

Etravirine

Clarithromycin exposure was decreased by etravirine; however, concentrations of the active metabolite, 14OHclarithromycin, were increased. Because 14OHclarithromycin has reduced activity against Mycobacterium avium complex (MAC), overall activity against this pathogen may be altered; therefore alternatives to clarithromycin should be considered for the treatment of MAC.

Fluconazole

Concomitant administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily to 21 healthy volunteers led to increases in the mean steadystate minimum clarithromycin concentration (Cmin) and area under the curve (AUC) of 33% and 18% respectively. Steady state concentrations of the active metabolite 14-OHclarithromycin were not significantly affected by concomitant administration of fluconazole. No clarithromycin dose adjustment is necessary.

Ritonavir

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg every eight hours and clarithromycin 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin Cmax increased by 31%, Cmin increased 182% and AUC increased by 77% with concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14-OHclarithromycin was noted. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered: For patients with CLCR 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. For patients with CLCR <30 mL/min the dose of clarithromycin should be decreased by 75%. Doses of

clarithromycin greater than 1 gm/day should not be coadministered with ritonavir.

Similar dose adjustments should be considered in patients with reduced renal function when ritonavir is used as a pharmacokinetic enhancer with other HIV protease inhibitors including atazanavir and saquinavir .

4.7 Pregnancy and lactation

Pregnancy

Should not prescribe clarithromycin to pregnant women without carefully weighing the benefits against risk,particularly during the first three months of pregnancy

Lactation

Clarithromycin is excreted into human breast milk , consult doctor before use.

4.8 Effects on ability to drive and use machines

There are no data on the effect of clarithromycin on the ability to drive or use machines. The potential for dizziness, vertigo, confusion and disorientation, which may occur with the medication, should be taken into account before patients drive or use machines.

4.9 Undesirable effects

Summary of the safety profile

The most frequent and common adverse reactions related to clarithromycin therapy for both adult and peadiatric 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.

Tabulated summary of adverse reactions

The following table displays adverse reactions reported in clinical trials and from postmarketing experience.

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 postmarketing experience; cannot be estimated from the available data)

System Organ Class	Frequency	Undesirable Effect
Infections and infestations	Uncommon	Candidiasis , vaginal infection
	Not known	Pseudomembranous colitis,erysipelas, erythrasma
Blood and lymphatic system	Uncommon	Leukopenia, neutropenia , eosinophilia
	Not known	Pseudomembranous colitis, erysipelas, erythrasma
Immune system disorders	Uncommon	hypersensitivity
	Not known	Anaphylactic reaction
Metabolism and nutrition disorders	Uncommon	Anorexia, decreased appetite
Psychiatric disorders	Common	Insomnia
	Uncommon	Anxiety
	Not known	Psychotic disorder, confusional state, depersonalisation, depression, disorientation, hallucination, abnormal dreams
Nervous system disorders	Common	Dysgeusia, headache, taste perversion
	Uncommon	Dizzines , tremor
	Not known	Convulsion, ageusia, parosmia, anosmia paraesthesia
Ear and labyrinth disorders	Uncommon	Vertigo, hearing impaired, tinnitus
	Not known	Deafness
Cardiac disorders	Uncommon	palpitations
Gastrointestinal disorders	Common	vomiting, dyspepsia, nausea, abdominal pain
	Uncommon	stomatitis, glossitis, abdominaldistension , constipation,dry mouth, eructation, flatulence,
	Not known	Pancreatitis acute, tongue discolouration, tooth Discolouration
Hepatobiliary disorders	Common	Liver function test abnormal
	Uncommon	Cholestasis , hepatitis , alanine aminotransferase increased, aspartate aminotransferase increased,

		gammaglutamyltransferase increased
	Not known	Jaundice hepatocellular
Skin and subcutaneous tissue disorders	Common	Rash, hyperhidrosis
	Uncommon	pruritus, urticaria,
	Not known	drug rash with eosinophilia and systemic symptoms (DRESS), acne HenochSchonlein purpura
Musculoskeletal and connective tissue disorders	Not known	Myopathy
Renal and urinary disorders	Not known	Renal failure, nephritis interstitial
General disorders and administration site conditions	Uncommon	Malaise ,asthenia, chest pain , chills , fatigue
Investigations	Uncommon	blood alkaline phosphatase increased , blood lactate dehydrogenase increased
	Not known	urine color abnormal

4.10 Overdose

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastrointestinal symptoms. . The symptoms described in connection with 8 grams of clarithromycin showed altered mental status, paranoid behavior, hypokalemia and hypoxemia. Adverse reactions accompanying overdose should be treated by the prompt elimination of unabsorbed drug and supportive measures. As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by hemodialysis or peritoneal dialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Clarithromycin is a semisynthetic derivative of erythromycin A. It exerts its antibacterial action by binding to the 50s ribosomal subunit of susceptible bacteria and suppresses protein synthesis. It is highly potent against a wide variety of aerobic and anaerobic grampositive and gramnegative organisms. The minimum inhibitory concentrations (MICs) of clarithromycin are generally twofold lower than the MICs of erythromycin.

The 14hydroxy metabolite of clarithromycin also has antimicrobial activity. The MICs of this metabolite are equal or twofold higher than the MICs of the parent compound, except for H. influenzae where the 14hydroxymetabolite is twofold more active than the parent compound.

5.2 Pharmacokinetic properties

Absorption

Clarithromycin is rapidly and well absorbed from the gastrointestinal tract after oral administration of Clarithromycin tablets. The microbiologically active metabolite 14hydroxyclarithromycin is formed by first pass metabolism. Clarithromycin may be given without regard to meals as food does not affect the extent of bioavailability of Clarithromycin tablets. Food does slightly delay the onset of absorption of clarithromycin and formation of the 14hydroxymetabolite

Distribution

When clarithromycin 500 mg is given three times daily, the clarithromycin plasma concentrations are increased with respect to the 500 mg twice daily dosage.

Clarithromycin provides tissue concentrations that are several times higher than the circulating drug levels. Increased levels have been found in both tonsillar and lung tissue. Clarithromycin is 80% bound to plasma proteins at therapeutic levels.

Clarithromycin also penetrates the gastric mucus. Levels of clarithromycin in gastric mucus and gastric tissue are higher when clarithromycin is coadministered with omeprazole than when clarithromycin is administered alone.

Metabolism and Excretion

Steady state is attained within 2 days of dosing. At 250 mg b.i.d. 15-20% of unchanged drug is excreted in the urine. With 500 mg b.i.d. daily dosing urinary excretion is greater (approximately 36%). The 14hydroxyclarithromycin is the major urinary metabolite and accounts for 10-15% of the dose. Most of the remainder of the dose is eliminated in the faeces, primarily via the bile. 5-10% of the parent drug is recovered from the faeces

5.3 Preclinical safety data

Not Applicable

6. Pharmaceutical particulars

6.1 List of Excipients

Sr No	Name of Ingredients	Specification
1	Microcrystalline cellulose	BP
2	Pregelatinized Starch	BP
3	Sodium starch glycollate	BP
4	Cross Carmellose Sodium	USP
5	Purified talc	BP
6	Silicon dioxide	USP
7	Sodium Lauryl Sulphate	BP
8	Magnesium stearate	BP
9	Ready to coat (Tartrazine Yellow)	IHS
10	Iso propyl Alcohol	BP
11	Dichloromethane	BP

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in a dry and dark place, below 30°C.

Keep out of the reach and sight of children.

6.5 Nature and contents of container

10 X 10's Al/PVC Blister

6.6 Instruction for use and handling

Not applicable

7. Marketing Authorization Holder

Astra lifecare (India) Pvt. Ltd

Plot No. 57/P, Sarkhej – Bavla Highway,

Post. Rajoda –382220, Taluka: Bavla,

Dist. Ahmedabad, India.

8. Marketing Authorization Number(s)

04570/3031/NMR/2016

9. Date of first authorization/renewal of the authorization

Jul 17, 2019

10. Date of revision of the text

Not applicable