1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

Attached Hereafter

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

INCLAR OD (Clarithromycin Extended Release Tablets USP)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated extended-release tablet contains
Clarithromycin USP 500mg

For a full list of Excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film Coated Extended Release Tablets.
Yellow colored film coated, oblong shaped and biconvex tablet with both sides plain.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults

Clarithromycin extended release tablets are indicated for the treatment of adults with mild to moderate infection caused by susceptible strains of the designated microorganisms in the conditions listed below:

- Acute maxillary sinusitis due to Haemophilus influenzae, Moraxella catarrhalis, or Streptococcus pneumoniae.
- Acute bacterial exacerbation of chronic bronchitis due to Haemophilus parainfluenzae, Haemophilus influenzae, Moraxella catarrhalis or Streptococcus pneumoniae.
- Community Acquired Pneumoniae due to Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Streptococcus pneumoniae, Chlamydia pneumoniae (TWAR), or Mycoplasma pneumoniae.
- Upper respiratory tract infections for example, sinusitis and pharyngitis.
- Skin and soft tissue infections of mild to moderate severity, for example folliculitis, cellulitis and erysipelas.

4.2 Posology and Method of Administration

Adults: The usual recommended dosage of Clarithromycin Extended-Release Tablets USP in adults is one 500 mg extended release tablet daily to be taken with food and tablets should be swallowed whole and not chewed, broken or crushed. In most severe infections, the dosage can be increased to two 500 mg extended release tablets daily. Dose must be taken at the same time every day. The usual duration of treatment is 7 to 14 days.

Children older than 12 years: As for adults.

Children younger than 12 years: Use of Clarithromycin Extended Release Tablets 500mg are not recommended for children younger than 12 years.

Clarithromycin may be administered without dosage adjustment in the presence of hepatic impairment if there is normal renal function. However, in the presence of severe renal impairment (creatinine clearance less than 30 mL/min) with or without coexisting hepatic impairment, the dosage is 250 mg once daily or 250 mg twice daily in more severe infections. Treatment should not be continued beyond 14 days in these patients. Because the tablet cannot be split, the dose cannot be reduced from 500 mg daily, Clarithromycin 500 mg Extended Release Tablets should not be used in this patient population.

	Clarithromycin Extended Release Tablets USP	
INFECTIONS	**Dosage (q24 h)**	**Duration (days)**
Pharyngitis /Tonsillitis due to	500 mg	7
S. Pyogenes		
Acute maxillary sinusitis due to	2x500 mg	14
H. influenzae		
M. catarrhalis		
S. pneumoniae		
Acute exacerbation of chronic bronchitis due to		
H. influenzae	2x500 mg	7
M. catarrhalis	2x500 mg	7
H. parainfluenzae	2x500 mg	7
S. pneumoniae	2x500 mg	7
Community-acquired Pneumonia due to		
H. influenzae	2x500 mg	7
M. catarrhalis	2x500 mg	7
H. parainfluenzae	2x500 mg	7
S. pneumoniae	2x500 mg	7
C. pneumoniae	2x500 mg	7
M. pneumoniae	2x500 mg	7
Uncomplicated skin and skin structure	500 mg	7
S. aureus		
S. pyogenes		

4.3 Contra-indications

Clarithromycin is contraindicated in patients with a known hypersensitivity to Clarithromycin, erythromycin, or any of the macrolide antibiotics.

As the dose cannot be reduced from 500mg daily, Clarithromycin Extended Release Tablets 500mg are contraindicated in patients with creatinine clearance less than 30 mL/min.

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, including torsades de pointe.

Clarithromycin should not be used concomitantly with HMG-CoA reductase inhibitors (statins), lovastatin or simvastatin, due to the risk of rhabdomyolysis. Treatment with these agents should be discontinued during clarithromycin treatment.
Clarithromycin should not be given to patients with hypokalaemia (risk of prolongation of QT-time).

Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment.

Concomitant administration of clarithromycin and colchicine is contraindicated in patients with renal or hepatic impairment.

4.4 Special Warnings and Special Precautions for Use

Precautions:

In the presence of severe renal impairment with or without coexisting hepatic impairment decreased dosage or prolonged dosing intervals may be appropriate.

General: Clarithromycin in combination with Ranitidine bismuth citrate therapy is not recommended in patients with creatinine clearance less than 25 mL/min.

Carcinogenesis, Impairment of Fertility:

Carcinogenesis: Long - term studies in animals have not been performed to evaluate the carcinogenic potential of Clarithromycin.

Impairment of Fertility: Fertility and reproduction studies have shown that daily doses of up to 160mg/kg/day (1.3 times the recommended maximum human dose based on mg/m^2) to male and female rats caused no adverse effects on the estrous cycle, fertility, parturition, or number and viability of offspring.

Pregnancy: There are no adequate and well - controlled studies in pregnant women. Clarithromycin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether Clarithromycin is excreted in human milk. It is known that Clarithromycin is excreted in the milk of lactating animals and that other drugs of this class are excreted in human milk.

Geriatric Use: In a steady-state study in which healthy elderly subjects (age 65 to 81 years old) were given 500 mg every 12 hours, the maximum serum concentrations and area under the curves of Clarithromycin and 14-OH Clarithromycin were increased compared to those achieved in healthy young adults.

These changes in pharmacokinetics parallel known age-related decreases in renal function. Dosage adjustment should be considered in elderly patients with severe renal impairment.

Elderly patients may be more susceptible to development of *torsades de pointes* arrhythmias than younger patients.

Most reports of acute kidney injury with calcium channel blockers metabolized by CYP3A4 (e.g., verapamil, amlodipine, diltiazem, nifedipine) involved elderly patients 65 years of age or older.

Warnings:
Clarithromycin should not be used in pregnant women except in clinical circumstances where no alternative therapy is appropriate, if pregnancy occurs while taking this drug the patient should be apprised of the potential hazard to the fetus. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including Clarithromycin and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of anti bacterial agents.

Hepatotoxicity

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. In some instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications. Symptoms of hepatitis can include anorexia, jaundice, dark urine, pruritus, or tender abdomen. Discontinue clarithromycin immediately if signs and symptoms of hepatitis occur.

QT Prolongation

Clarithromycin has been associated with prolongation of the QT interval and infrequent cases of arrhythmia. Cases of *torsades de pointes* have been spontaneously reported during postmarketing surveillance in patients receiving clarithromycin. Fatalities have been reported. Clarithromycin should be avoided in patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents. Elderly patients may be more susceptible to drug-associated effects on the QT interval.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Serious adverse reactions have been reported in patients taking clarithromycin concomitantly with CYP3A4 substrates. These include colchicine toxicity with colchicine; rhabdomyolysis with simvastatin, lovastatin, and atorvastatin; and hypotension and acute kidney injury with calcium channel blockers metabolized by CYP3A4 (e.g., verapamil, amlodipine, diltiazem, nifedipine). Most reports of acute kidney injury with calcium channel blockers metabolized by CYP3A4 involved elderly patients 65 years of age or older.

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

Colchicine

Life-threatening and fatal drug interactions have been reported in patients treated with clarithromycin and colchicine. Clarithromycin is a strong CYP3A4 inhibitor and this interaction may occur while using both drugs at their recommended doses. If co-administration of clarithromycin and colchicine is necessary in patients with normal renal and hepatic function, the dose of colchicine should be reduced. Patients should be monitored for clinical symptoms of colchicine toxicity. Concomitant administration of clarithromycin and colchicine is contraindicated in patients with renal or hepatic impairment.

Benzodiazepines

Increased sedation and prolongation of sedation have been reported with concomitant administration of clarithromycin and triazolobenzodiazepines, such as triazolam, and midazolam.

Oral Hypoglycemic Agents/Insulin

The concomitant use of clarithromycin and oral hypoglycemic agents and/or insulin can result in significant hypoglycemia. With certain hypoglycemic drugs such as nateglinide, pioglitazone, repaglinide and rosiglitazone, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause hypoglycemia when used concomitantly. Careful monitoring of glucose is recommended.

Oral Anticoagulants

There is a risk of serious hemorrhage and significant elevations in 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.

HMG-CoA 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. Cases of rhabdomyolysis have been reported in patients taking clarithromycin concomitantly with these statins. 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 atorvastatin or pravastatin cannot be avoided, atorvastatin dose should not exceed 20 mg daily and pravastatin dose should not exceed 40 mg daily. Use of a statin that is not dependent on CYP3A metabolism (e.g.fluvastatin) can be considered. It is recommended to prescribe the lowest registered dose if concomitant use cannot be avoided.

***Clostridium difficile* Associated Diarrhea**

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Clarithromycin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

Acute Hypersensitivity Reactions

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, Stevens- Johnson Syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), and Henoch-Schonlein purpura clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

Combination Therapy with Other Drugs

For information about warnings of other drugs indicated in combination with Clarithromycin, refer to the drug interaction information of their package inserts.

4.6 Pregnancy and Lactation

The safety of clarithromycin during pregnancy and breast feeding of infants has not been established. Based on variable results obtained from studies in mice, rats, rabbits and monkeys, the possibility of adverse effects on embryo foetal development cannot be excluded. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risk. Clarithromycin is excreted into human breast milk

4.7 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

4.8 Undesirable Effects

The majority of side effects observed in clinical trials were of a mild and transient nature. Fewer than 3% of adult patients without mycobacterial infections and fewer than 2% of pediatric patients without mycobacterial infections discontinued therapy because of drug-related side effects. Fewer than 2% of adult patients taking Clarithromycin tablets OD discontinued therapy because of drug - related side effects. The most frequently reported events in adults taking Clarithromycin tablets were diarrhea (3%), nausea (3%), abnormal

taste (3%), dyspepsia (2%), abdominal pain/discomfort (2%), and headache (2%). Most of these events were described as mild or moderate in severity. Of the reported adverse events, only 1% was described as severe.

Adverse Reactions Observed During Clinical Trials of Clarithromycin

The following adverse reactions were observed in clinical trials with clarithromycin at a rate greater than or equal to 1%:

Gastrointestinal Disorders: Diarrhea, vomiting, dyspepsia, nausea, abdominal pain

Hepatobiliary Disorders: Liver function test abnormal

Immune System Disorders: Anaphylactoid reaction

Infection and Infestations: Candidiasis

Nervous System Disorders: Dysgeusia, headache

Psychiatric Disorders: Insomnia

Skin and Subcutaneous Tissue Disorders: Rash

Immune System Disorders : Hypersensitivity

Infections and Infestations: Cellulitis, gastroenteritis, infection, vaginal infection

***Investigations*:** Blood bilirubin increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, albumin globulin ratio abnormal

Metabolism and Nutrition Disorders: Anorexia, decreased appetite

Musculoskeletal and Connective Tissue Disorders: Myalgia, muscle spasms, nuchal rigidity

Nervous System Disorders: Dizziness, tremor, loss of consciousness, dyskinesia, somnolence

Psychiatric Disorders: Anxiety, nervousness

Renal and Urinary Disorders: Blood creatinine increased, blood urea increased

Respiratory, Thoracic and Mediastinal Disorders: Asthma, epistaxis, pulmonary embolism

Skin and Subcutaneous Tissue Disorders: Urticaria, dermatitis bullous, pruritus, hyperhidrosis, rash maculo-papular.

4.9 Overdose

Overdosage of Clarithromycin can cause gastrointestinal symptoms such as abdominal pain, vomiting, nausea, and diarrhea

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Clarithromycin exerts its antibacterial action by binding to the 50S ribosomal subunit of susceptible microorganisms resulting in inhibition of protein synthesis. Clarithromycin is active in vitro against a variety of aerobic and anaerobic gram positive and gram - negative microorganisms as well as most *Mycobacterium avium* complex (MAC) microorganisms. Additionally, the 14-OH Clarithromycin metabolite also has clinically significant antimicrobial activity. The 14-OH Clarithromycin is twice as active against Haemophilus influenzae microorganisms as the parent compound. However, for *Mycobacterium avium* complex (MAC) isolates the 14-OH metabolite is 4 to 7 times less active than Clarithromycin. The clinical significance of this activity against *Mycobacterium avium* complex is unknown. Clarithromycin has been shown to be active against most strains like *Staphylococcus aureus, Staphylococcus pneumoniae, Haemophilus parainfluenzae, Streptococcus pyogenes, Haemophilus influenzae, Mycoplasma pneumoniae, Mycobacterium avium* complex (MAC) both in vitro and in clinical infections. Beta - lactamase production should have no effect on Clarithromycin activity.

Note: Most strains of methicillin-resistant and oxacillin resistant staphylococci are resistant to Clarithromycin.

5.2 Pharmacokinetic Properties

Clarithromycin is rapidly absorbed from the gastrointestinal tract after oral administration. The kinetics of orally administered extended-release clarithromycin have been studied in adult humans and compared with clarithromycin 250mg and 500mg immediate release tablets. The extent of absorption was found to be equivalent when equal total daily doses were administered. The absolute bioavailability is approximately 50%. Food also increases the Clarithromycin peak plasma concentration by about 24%, but does not affect the extent of Clarithromycin bioavailability. Food does not affect the onset of formation of the antimicrobially active metabolite, 14-OH Clarithromycin or its peak plasma concentration but does slightly decrease the extent of metabolite formation, indicated by an 11% decrease in area under the plasma concentration-time curve (AUC). Therefore, Clarithromycin tablets may be given without regard to food. While the extent of formation of 14-OH Clarithromycin following administration of Clarithromycin OD tablets (2 x 500 mg once daily) is not affected by food. Administration under fasting conditions is associated with approximately 30% lower Clarithromycin AUC relative to administration with food. Therefore, Clarithromycin OD tablets should be taken with food. The pharmacokinetics of Clarithromycin was also altered in subjects with impaired renal function.

The pharmacokinetic behaviour of clarithromycin is non-linear. In fed patients given 500mg clarithromycin extended-release daily, the peak steady state plasma concentration of clarithromycin and 14 hydroxy clarithromycin were 1.3 and 0.48µg/mL, respectively.

When the dosage was increased to 1000mg daily, these steady-state values were 2.4µg/mL and 0.67µg/mL respectively. Elimination half-lives of the parent drug and metabolite were approximately 5.3 and 7.7 hours respectively. The apparent half-lives of both clarithromycin and its hydroxylated metabolite tended to be longer at higher doses.

Urinary excretion accounted for approximately 40% of the clarithromycin dose. Faecal elimination accounts for approximately 30%.

5.3 Preclinical Safety Data

In repeated dose studies, clarithromycin toxicity was related to dose and duration of treatment. The primary target organ was the liver in all species, with hepatic lesions seen after 14 days in dogs and monkeys. Systemic exposure levels associated with this toxicity are not known but toxic mg/kg doses were higher than the dose recommended for patient treatment.

No evidence of mutagenic potential of clarithromycin was seen during a range of in vitro and in vivo tests.

Fertility and reproduction studies in rats have shown no adverse effects. Teratogenicity studies in rats (Wistar (p.o.) and Sprague-Dawley (p.o. and i.v.)), New Zealand White rabbits and cynomolgous monkeys failed to demonstrate any teratogenicity from clarithromycin. However, a further similar study in Sprague-Dawley rats indicated a low (6%) incidence of cardiovascular abnormalities which appeared to be due to spontaneous expression of genetic changes. Two mouse studies revealed a variable incidence (3-30%) of cleft palate and in monkeys embryonic loss was seen but only at dose levels which were clearly toxic to the mothers.

No other toxicological findings considered to be of relevance to the dose level recommended for patient treatment have been reported.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablet core

Lactose Monohydrate
Hydroxypropyl methylcellulose (Hypromellose)
Hydroxypropyl Methyl Cellulose Phthalate (Hypromellose Phthalate)
Purified Talc
Magnesium Stearate

Film Coat

Opadry II Yellow 31G52300 (consists of Hypromellose, Lactose Monohydrate, Titanium Dioxide (E171), Polyethylene Glycol, Talc and Quinoline Yellow Aluminium Lake (E104)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

48 months

6.4 Special Precautions for Storage

Store below 30°C. Protect from light and moisture.

KEEP ALL MEDICINE OUT OF REACH OF CHILDREN

6.5 Nature and Contents of Container

Blister pack of 7 tablets using Rigid PVC film coated with PVdC Pharma grade (clear, 90gsm coated) and Printed Aluminum foil. Such one blister pack is packed in a carton along with insert. Such 10 inner cartons are packed in an outer carton.

6.6 Special precautions for disposal

No special requirements

Administrative Data

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF (PARTIAL) REVISION OF THE TEXT

March 2018