SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Clarithromycin 250 mg Film Coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Clarithromycin 250 mg Film Coated Tablets: Clarithromycin 250 mg/tablet

For excipients see section 6.1.

3 PHARMACEUTICAL FORM

Clarithromycin 250 mg Film Coated Tablets:

A yellow coloured, elliptical, biconvex film-coated tablet with smooth surface containing 250 mg of clarithromycin.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Clarithromycin Tablets are indicated for treatment of infections caused by susceptible organisms. Indications include:

Lower respiratory tract infections for example, acute and chronic bronchitis, and pneumonia.

Upper respiratory tract infections for example, sinusitis and pharyngitis.

Clarithromycin Tablets are appropriate for initial therapy in community acquired respiratory infections and have been shown to be active in vitro against common and atypical respiratory pathogens as listed in section 5.1. “Pharmacodynamic properties”.

Clarithromycin Tablets are also indicated in skin and soft tissue infections of mild to moderate severity.

Clarithromycin Tablets in the presence of acid suppression effected by omeprazole or lansoprazole are also indicated for the eradication of *H. pylori* in patients with duodenal ulcers.
See Dosage and Administration section.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.
Clarithromycin tablets are indicated in adults and children 12 years and older

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 for 7 days although this may be increased to 500 mg twice daily for up to 14 days in severe infections.
Children younger than 12 years: Use of clarithromycin tablets is not recommended for children younger than 12 years. Use clarithromycin Paediatric Suspension.
Children older than 12 years: As for adults.
The usual duration of treatment is 6 to 14 days.

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

Triple Therapy (7 - 14 days)
Clarithromycin 500 mg twice daily and lansoprazole 30 mg twice daily should be given with amoxycillin 1000 mg twice daily for 7 - 14 days.

Triple Therapy (7 days)
Clarithromycin 500 mg twice daily and lansoprazole 30 mg twice daily should be given with metronidazole 400 mg twice daily for 7 days.

Triple Therapy (7 days)
Clarithromycin 500 mg twice daily and omeprazole 40 mg daily should be given with amoxycillin 1000 mg twice daily or metronidazole 400 mg twice daily for 7 days.

Triple Therapy (10 days)

Clarithromycin 500 mg twice daily should be given with amoxycillin 1000 mg twice daily and omeprazole 20 mg daily for 10 days.

Dual Therapy (14 days)

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 for 14 days.

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.

Clarithromycin Tablets may be given without regard to meals as food does not affect the extent of bioavailability.

4.3 Contraindications

Clarithromycin is contra-indicated in patients with known hypersensitivity to clarithromycin, other macrolide antibiotics or to any of the excipients in the tablet.

Clarithromycin and ergot derivatives must not be co-administered.

Concomitant administration of clarithromycin and any of the following drugs is contra-indicated: cisapride, pimozide and terfenadine. Elevated cisapride, pimozide and terfenadine levels have been reported in patients receiving either of these drugs and clarithromycin concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and Torsade de Pointes. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

Clarithromycin is contra-indicated in patients with hypokaliemia. This may result in QT prolongation.

4.4 Special warnings and precautions for use

Clarithromycin is principally excreted by the liver and kidney. Caution should be exercised in administering this antibiotic to patients with impaired hepatic or renal function.

Prolonged or repeated used of clarithromycin may result in an overgrowth of non-susceptible bacteria or fungi. If super-infection occurs, clarithromycin should be discontinued and appropriate therapy instituted.

H. pylori organisms may develop resistance to clarithromycin.

4.5 Interaction with other medicinal products and other forms of interaction

As with other macrolide antibiotics the use of clarithromycin in patients concurrently taking drugs metabolised by the cytochrome P 450 system (eg. warfarin, ergot alkaloids, triazolam, midazolam, disopyramide, lovastatin, rifabutin, phenytoin, valproate, cyclosporin, tacrolimus, rifampicin, cisapride, methyl prednisolone, vinblastine, sildenafil, hexobarbital, alfentanil, pimozide, terfenadine, alprazolam, cilostazol and chinidin) may be associated with elevations in serum levels of these other drugs.

HMG-CoA reductase inhibitors:

Rhabdomyolysis, co-incident with the co-administration of clarithromycin, and HMG-CoA reductase inhibitors, such as lovastatin and simvastatin has been reported.

Further interactions:

The administration of clarithromycin to patients who are receiving theophylline has been associated with an increase in serum theophylline levels and potential theophylline toxicity.

As mentioned above the use of clarithromycin in patients receiving warfarin may result in potentiation of the effects of warfarin. Prothrombin time should be frequently monitored in these patients.

The effects of digoxin may be potentiated with concomitant administration of Clarithromycin Tablets. Monitoring of serum digoxin levels should be considered.

Clarithromycin may potentiate the effects of carbamazepine due to a reduction in the rate of excretion.

Simultaneous oral administration of Clarithromycin Tablets and zidovudine to HIV infected adult patients may result in decreased steady-state zidovudine levels. This can be largely avoided by staggering the doses of Clarithromycin Tablets and zidovudine by 1 - 2 hours. No such reaction has been reported in children.

Ritonavir increases the area under the curve (AUC), C_{max} and C_{min} of clarithromycin when administered concurrently. 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 CL_{CR} 30 to 60 ml/min the dose of clarithromycin should be reduced by 50%. For patients with $CL_{CR} < 30$ ml/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1g/day should not be co-administered with ritonavir.

Although the plasma concentrations of clarithromycin and omeprazole may be increased when they are administered concurrently, no adjustment to the dosage is necessary. At the dosages recommended, there is no clinically significant interaction between clarithromycin and lansoprazole. Increased plasma concentrations of clarithromycin may also occur when it is co-administered with aluminium oxide/magnesium hydroxide-antacids or ranitidine. No adjustment to the dosage is necessary.

Macrolides have been reported to have an effect on the metabolism of terfenadine/astemizole, in which case the terfenadine/astemizole values are elevated, which has, in individual cases, been shown to cause cardiac arrhythmias. Similar effects have also been reported with combined use of astmizole and other macrolides.

A concomitant administration of macrolide antibiotics with cyclosporine and bromocriptine may result in an increase of plasma levels of cyclosporine and bromocriptine. Consequently the dose of cyclosporine and bromocriptine needs to be decreased.

A potential cross-resistance of bacterial strains against clarithromycin and other macrolide antibiotics such as erythromycin and clindamycin needs to be considered. The concomitant administration of products belonging to this compound class is therefore not recommended.

There have been postmarketed reports of Torsade de Points occurring with the concurrent use of clarithromycin and quinidine or disopyramide. Levels of these medications should be monitored during clarithromycin therapy.

Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). Clarithromycin and other macrolides are known to inhibit CYP3A and Pgp. When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine. Patients should be monitored for clinical symptoms of colchicine toxicity

4.6 Pregnancy and lactation

The safety of clarithromycin during pregnancy and breast feeding of infants has not been established. Clarithromycin Tablets should thus not be used during pregnancy or lactation unless the benefit is considered to outweigh the risk. Some animal studies have suggested an embryotoxic effect, but only at dose levels which are clearly toxic to mothers. Clarithromycin has been found in the milk of lactating animals and in human breast milk.

4.7 Effects on ability to drive and use machines

Although clarithromycin is not expected to affect driving ability directly, side effects such as dizziness and vertigo may interfere with driving.

4.8 Undesirable effects

Infections and infestations:
Oral monilla, genital candidiasis

Blood and lymphatic system disorders:
Isolated cases of leukopenia and thrombocytopenia have been reported.

Immune system disorders:
Allergic reactions ranging from urticaria, mild skin eruptions and angioedema to anaphylaxis and rarely Stevens-Johnson syndrome / toxic epidermal necrolysis.

Metabolic disorders:
There have been rare reports of hypoglycaemia, some of which have occurred in patients on concomitant oral hypoglycaemic agents or insulin.

Sense organs disorders (Eye disorders, Ear and labyrinth disorders, taste):
Reports of alteration of the sense of smell, usually in conjunction with taste perversion have also been received. There have been reports of hearing loss with clarithromycin which is usually reversible on withdrawal of therapy. Tinnitus.

There have been very rare reports of uveitis mainly in patients treated with concomitant rifabutin, most of these were reversible.

Psychiatric and nervous system disorders:
There have been reports of transient central nervous system side-effects including headache, dizziness, vertigo, anxiety, insomnia, bad dreams, confusion, disorientation, hallucinations, psychosis and depersonalisation. Convulsions have been reported rarely.

Cardiac disorders:
As with other macrolides, QT prolongation, ventricular tachycardia and Torsade de Pointes have been rarely reported with clarithromycin.

Gastrointestinal disorders:
Nausea, dyspepsia, diarrhoea, vomiting, abdominal pain, paraesthesia, glossitis and tongue discolouration. There have been reports of tooth discolouration in patients treated with clarithromycin. Tooth discolouration is usually reversible with professional dental cleaning. Stomatitis has been reported.

Pseudomembranous colitis has been reported rarely with clarithromycin, and may range in severity from mild to life threatening.

Pancreatitis has been reported rarely.

Hepatobiliary disorders:
As with other macrolides, hepatic dysfunction (which is usually reversible) including altered liver function tests, hepatitis and cholestasis with or without jaundice, has

been reported. Dysfunction may be severe and very rarely fatal hepatic failure has been reported.

Musculoskeletal and connective tissue disorders:
Arthralgia, myalgia.
Rhabodomyolysis can occur in rare cases during concomitant administration of clarithromycin and HMG-CoA reductase inhibitor, lovastatin and simvastatin.

Specific side effects have been observed in HIV patients treated for mycobacterial infections.

Renal and urinary disorders:
Cases of interstitial nephritis and renal failure have been reported rarely.

Increased investigations:
Increased serum creatinine, altered liver function tests.
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 (see Sections 4.4 and 4.5).

4.9 Overdose

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastro-intestinal symptoms. One patient who had a history of bipolar disorder ingested 8 grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokaliemia and hypoxemia. Adverse reactions accompanying overdosage should be treated by gastric lavage and supportive measures. As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: macrolides

ATC-Code: J01FA09

Mode of Action

Clarithromycin is a semi-synthetic derivative of erythromycin A. It exerts its antibacterial action by binding to the 50s ribosomal sub-unit of susceptible bacteria and suppresses protein synthesis. It is highly potent against a wide variety of aerobic and anaerobic gram-positive and gram-negative organisms. The minimum inhibitory concentrations (MICs) of clarithromycin are generally two-fold lower than the MICs of erythromycin.

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

Mechanisms of resistance

Resistance of gram-positive organisms to the macrolides usually involves an alteration of the antimicrobial binding site. The MLS_B type of resistance, which may be constitutive or induced by exposure to certain macrolides in staphylococci and which is inducible in streptococci, is mediated by a variety of acquired genes (*erm* family) encoding methylases targeted at the peptidyl transferase centre of 23S ribosomal RNA. Methylation impedes binding of antibacterials to the ribosome and gives rise to cross-resistance to macrolides (all macrolides when constitutive), lincosamides and type B streptogramins but not to type A streptogramins. Less frequent mechanisms of resistance include antimicrobial degradation by inactivating enzymes such as esterase and active efflux of the antimicrobial from the bacteria.

Gram negative organisms may be intrinsically resistant to the macrolides because of the inability of the macrolide to effectively penetrate the outer cell membrane;

macrolides having a better penetration may have activity against some gram-negative organisms.

Gram-negative organisms may also produce ribosomal methylase

Breakpoints

Breakpoint Concentrations

According to BSAC (January 2005) the following breakpoints have been defined for clarithromycin:

Organism	MIC Breakpoint Concentration (mg/L)	
	Susceptible ≤	Resistant >
Staphylococci	0.5	0.5
ß-Haemolytic Streptococci*	0.5	0.5
S.pneumoniae	0.5	0.5
*M. catarrhalis**	0.5	0.5
*H. influenzae**	0.5	16**

* Active metabolite not taken into consideration

** Breakpoints for H. influenzae; strains with MICs below the low breakpoint are susceptible, those with MICs above the high breakpoint are resistant, others are intermediate

The following tentative MIC breakpoints have been defined for clarithromycin:

H. Pylori ≤ 1 mg/L susceptible, > 2 mg/L resistant.

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 the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

The susceptibility pattern of various micro-organisms to clarithromycin is presented below:

Commonly susceptible species
Aerobic Gram-negative microorganisms
Moraxella catarrhalis
Anaerobic microorganisms
Peptococcus *species*
Peptostreptococcus *species*
Propionibacterium acnes
Clostridium perfringens
Other microorganisms
Chlamydia pneumoniae
Legionella pneumophila
Mycoplasma pneumoniae
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
Staphylococcus aureus
Staphylococcus aureus *(methicillin-resistant)**
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes
Aerobic Gram-negative microorganisms
Haemophilus influenzae

*** Resistance to macrolides among MRSA is commonly more than 50% in the EU and affects nearly all strains in some areas.**

5.2 Pharmacokinetic properties

Clarithromycin is rapidly and well absorbed from the gastro-intestinal tract after oral administration of Clarithromycin Tablets. The microbiologically active metabolite 14-hydroxyclarithromycin is formed by first pass metabolism. Clarithromycin Tablets 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 14-hydroxymetabolite. The pharmacokinetics of clarithromycin are non linear; however, 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 14-hydroxyclarithromycin 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.

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

Clarithromycin 250 mg Film Coated Tablets provide 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 Tablets also penetrates the gastric mucus. Levels of clarithromycin in gastric mucus and gastric tissue are higher when clarithromycin is co-administered with omeprazole than when clarithromycin is administered alone.

5.3 Preclinical safety data

In acute mouse and rat studies, the median lethal dose was greater than the highest feasible dose for administration (5 g/kg BW).

In repeated dose studies, toxicity was related to dose, duration of treatment and species. Dogs were more sensitive than primates or rats. The major clinical signs at toxic doses included emesis, weakness, reduced food consumption and weight gain, salivation, dehydration and hyperactivity. In all species the liver was the primary target organ at toxic doses. Hepatotoxicity was detectable by early elevations of liver function tests. Discontinuation of the drug generally resulted in a return to or toward normal results. Other tissues less commonly affected included the stomach, thymus and other lymphoid tissues and the kidneys. At near therapeutic doses, conjunctival injection and lacrimation occurred only in dogs. At a massive dose of 400 mg/kg/day, some dogs and monkeys developed corneal opacities and/or oedema.

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 embryonic loss was seen in monkeys but only at dose levels which were clearly toxic to the mothers.

6.0 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium
Starch pregelatinised
Silicon dioxide
Povidone
Stearic acid
Magnesium stearate

Talc
Microcrystalline cellulose
Propylene glycol

Coating:
Quinoline Yellow Aluminium Lake (E104)
Vanillin
Propylene Glycol (E1520)
Hydroxypropyl Cellulose
Sorbic Acid (E200)
Titanium Dioxide (E171)
Hypromellose (E464)
Polysorbate 80 (E433)

6.2 Incompatibilities

None known.

6.3 Shelf life

42 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Pack sizes are 10, 12, 14, 20, 30, 50, 500 tablets in blister packs with outer pack and package leaflet.

All pack sizes may not be marketed.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Strandhaven Limited T/A Somex Pharma, 600 High Road, Ilford, Essex, IG3 8BS, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 15764/0039

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11/07/2008

10 DATE OF REVISION OF THE TEXT

23/03/2018