SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Karin 250 and 500 mg coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Karin 250 tablet contains 250 mg of clarithromycin.
Each Karin 500 tablet contains 500 mg of clarithromycin.

Excipients with known effect:
Karin contains sodium. For further information see section 4.4.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated tablets.

Karin 250 is an oblong, capsule-shaped, pink film coated tablet with a break-line on one side.
Karin 500 is an oblong, oval, pink film coated tablet with a break-line on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Karin is indicated in the treatment of infections caused by one or more 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.

Karin is appropriate for initial therapy in community acquired respiratory infections and has been shown to be active in vitro against common and atypical respiratory pathogens as listed in the microbiology section.

Karin is also indicated in:

- skin and soft tissue infections of mild to moderate severity.
- combination with proton pump inhibitor for the eradication of H. Pylori in patients with proven duodenal ulcer.
- treatment of Mycobacterium Avium Complex infection in AIDS patients.

4.2 Posology and method of administration

The recommended dosages of Karin tablets for the treatment of mild to moderate infections in adults are listed in TABLE 1.

TABLE 1. Adult Dosage Guidelines

Infection	Dosage (every 12 hours)	Duration (days)
Acute bacterial exacerbation of chronic bronchitis	250 to 500 mg[a]	7[b]-14
Acute maxillary sinusitis	500 mg	14
Community-acquired pneumonia	250 mg	7[c]-14
Pharyngitis/Tonsillitis	250 mg	10
Uncomplicated skin and skin structure infections	250 mg	7-14
Treatment and prophylaxis of disseminated Mycobacterium avium disease	500 mg[e]	
H.pylori eradication to reduce the risk of duodenal ulcer recurrence with amoxicillin and omeprazole or lansoprazole	500 mg	10-14
H.pylori eradication to reduce the risk of duodenal ulcer recurrence with omeprazole	500 mg every 8 hours	14

[a] For M. catarrhalis and S. pneumoniae use 250 mg. For H. influenzae and H. parainfluenzae, use 500 mg.
[b] For H parainfluenzae, the duration of therapy is 7 days.
[c] For H. influenzae, the duration of therapy is 7 days.
[d]therapy should continue if clinical response is observed. Karin can be discontinued when the patient is considered at low risk of disseminated infection.

Combination Dosing Regimens for H. pylori Infection

Triple therapy: clarithromycin/lansoprazole/amoxicillin

The recommended adult dosage is Karin 500 mg tablets, 30 mg lansoprazole, and 1 gram amoxicillin, all given every 12 hours for 10 or 14 days.

Triple therapy: clarithromycin/omeprazole/amoxicillin

The recommended adult dosage is Karin 500 mg tablets, 20 mg omeprazole, and 1 gram amoxicillin; all given every 12 hours for 10 days. In patients with an ulcer present at the time of initiation of therapy, an additional 18 days of omeprazole 20 mg once daily is recommended for ulcer healing and symptom relief.

Dual therapy: clarithromycin/omeprazole
The recommended adult dosage is Karin 500 mg tablets given every 8 hours and 40 mg omeprazole given once every morning for 14 days. An additional 14 days of omeprazole 20 mg once daily is recommended for ulcer healing and symptom relief.

Pediatric Dosage
The recommended daily dosage is 15 mg/kg/day divided every 12 hours for 10 days (up to the adult dose). Refer to dosage regimens for mycobacterial infections in pediatric patients for additional dosage information.

Dosage Regimens for Mycobacterial Infections
For the treatment of disseminated infection due to Mycobacterium avium complex (MAC), Karin tablets are recommended as the primary agents.
Karin tablets should be used in combination with other antimycobacterial drugs (e.g. ethambutol) that have shown in vitro activity against MAC or clinical benefit in MAC treatment.

Adult Patients
For treatment and prophylaxis of mycobacterial infections in adults, the recommended dose of Karin tablets is 500 mg every 12 hours.

Pediatric Patients
For treatment and prophylaxis of mycobacterial infections in pediatric patients, the recommended dose is 7.5 mg/kg every 12 hours up to 500 mg every 12 hours.

Karin tablets therapy should continue if clinical response is observed. Karin tablets can be discontinued when the patient is considered at low risk of disseminated infection.

Dosage Adjustment in Patients with Renal Impairment
See TABLE 2 for dosage adjustment in patients with moderate or severe renal impairment with or without concomitant atazanavir or ritonavir-containing regimens.

TABLE 2. Karin Tablets Dosage Adjustments in Patients with Renal Impairment

	Recommended Dosage Reduction
Patients with severe renal impairment (CLcr of <30 mL/min).	Reduce the dosage by 50%
Patients with moderate renal impairment (CLcr of 30 to 60 mL/min) taking concomitant atazanavir or ritonavir-containing	Reduce the dosage by 50%
Patients with severe renal impairment (CLcr of <30 mL/min) taking concomitant atazanavir or ritonavir- containing regimens.	Reduce the dosage by 75%

Dosage Adjustment Due to Drug Interactions
Decrease the dose of Karin tablets by 50 % when co-administered with atazanavir.

4.3 Contraindications

Karin is contraindicated in patients with known hypersensitivity to the active substance, macrolide antibiotic drugs or to any of the excipients listed in section 6.1.

Concomitant administration of Karin and any of the following drugs is contraindicated: astemizole, cisapride, domperidone, pimozide, terfenadine as this may result in QT prolongation and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsades de pointe (see section 4.5).

Concomitant administration with ticagrelor, ivabradine or ranolazine is contraindicated.

Concomitant administration of Karin and ergot alkaloids (e.g. ergotamine or dihydroergotamine is contraindicated, as this may result in ergot toxicity.

Karin should not be given to patients with history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including torsades de pointe (see sections 4.4 and 4.5).

Karin should not be used concomitantly with HMG-CoA reductase inhibitors (statins) that are extensively metabolized by CYP3A4 (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis. (see section 4.4 and 4.5).

Concomitant administration of Karin and lomitapide is contraindicated (see section 4.5).

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

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

As with other strong CYP3A4 inhibitors, Karin should not be used in patients taking colchicine.

Concomitant administration of Karin and oral midazolam is contraindicated (see section 4.5).

Concomitant administration of Karin and ivabradine is contraindicated, as this may result in increased plasma exposure of ivabradine (see section 4.5).

4.4 Special warnings and precautions for use

The physician should not prescribe Karin to pregnant women without carefully weighing the benefits against risk, particularly during the first three months of pregnancy (see section 4.6).

Caution is advised in patients with severe renal insufficiency (see section 4.2).

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

Cases of fatal hepatic failure (see section 4.8) 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 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, which may lead to overgrowth of *C. difficile.* CDAD must be considered in all patients who present with diarrhea 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 Karin 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 (see section 4.5). Concomitant administration of Karin and colchicine is contraindicated (see section 4.3).

Caution is advised regarding concomitant administration of Karin and triazolobenzodiazepines, such as triazolam, and intravenous or oromucosal midazolam (see section 4.5).

Cardiovascular events

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsade de pointes, have been seen in treatment with macrolides including clarithromycin (see section 4.8). Therefore, as the following situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes), Karin should be used with caution in the following patients:

- Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia,
- Patients with electrolyte disturbances. Karin must not be given to patients with hypokalaemia (see section 4.3).
- Patients concomitantly taking other medicinal products associated with QT prolongation (see section 4.5).
- Concomitant administration of Karin with astemizole, cisapride, pimozide and terfenadine is contraindicated (see section 4.3).
- Karin must not be used in patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia (see section 4.3).

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 Karin.

Pneumonia: In view of the emerging resistance of *Streptococcus pneumoniae* to macrolides, it is important that sensitivity testing be performed when prescribing Karin for community-acquired pneumonia. In hospital- acquired pneumonia, Karin 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)), Karin therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

Karin should be used with caution when administered concurrently with medications that induce the cytochrome CYP3A4 enzyme (see section 4.5).

HMG-CoA Reductase Inhibitors (statins): Concomitant use of Karin with lovastatin or simvastatin is contraindicated (see section 4.3). Caution should be exercised when prescribing Karin 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 Karin 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 (see section 4.5).

Oral hypoglycemic agents/Insulin: The concomitant use of Karin and oral hypoglycemic agents (such as sulphonylurias) and/or insulin can result in significant hypoglycemia. Careful monitoring of blood glucose is recommended (see section 4.5).

Oral anticoagulants: There is a risk of serious hemorrhage and significant elevations in International Normalized Ratio (INR) and prothrombin time when Karin is co-administered with warfarin (see section 4.5).
Caution should be exercised when Karin is co-administered with direct acting oral anticoagulants such as dabigatran, rivaroxaban, apixaban and edoxaban, particularly to patients at high risk of bleeding (see section 4.5).
INR and prothrombin times should be frequently monitored while patients are receiving Karin and oral anticoagulants concurrently.

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

Long-term use may, as with other antibiotics, result in colonization 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 Karin and other macrolide drugs, as well as lincomycin and clindamycin.

Karin contains sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

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

Astemizole, cisapride, domperidone, pimozide, 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 (see section 4.3).

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 (see section 4.3). In one study in 14 healthy volunteers, the concomitant administration of clarithromycin and terfenadine resulted in a two to three fold increase 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. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

Ergotamine/dihydroergotamine
Postmarketing reports indicate that co-administration 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 Karin and these medicinal products is contraindicated (see section 4.3).

Oral midazolam
When midazolam was co-administered with Karin tablets (500 mg twice daily), midazolam AUC was increased 7-fold after oral administration of midazolam. Concomitant administration of oral midazolam and Karin is contraindicated.

HMG-CoA reductase inhibitors (statins)
Concomitant use of Karin with lovastatin or simvastatin is contraindicated (see section 4.3) as these statins are extensively metabolized by CYP3A4 and concomitant treatment with Karin increases their plasma concentration, which increases the risk of myopathy, including rhabdomyolysis. Reports of rhabdomyolysis have been received for patients taking clarithromycin concomitantly with these statins. If treatment with Karin cannot be avoided, therapy with lovastatin or simvastatin must be suspended during the course of treatment.

Caution should be exercised when prescribing Karin with statins. In situations where the concomitant use of Karin 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.

Concomitant administration of Karin with lomitapide is contraindicated due to the potential for markedly increased transaminases (see section 4.3).

Hydroxychloroquine and chloroquine
Karin should be used with caution in patients receiving these medicines known to prolong the QT interval due to the potential to induce cardiac arrhythmia and serious adverse cardiovascular events.

Effects of other medicinal products on Karin
Drugs that are inducers of CYP3A (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, St. John's wort) may induce the metabolism of Karin. This may result in sub-therapeutic levels of Karin 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 Karin (see also the relevant product information for the CYP3A4 inhibitor administered). Concomitant administration of rifabutin and Karin resulted in an increase in rifabutin, and decrease in Karin serum levels together with an increased risk of uveitis.

The following active substances are known or suspected to affect circulating concentrations of Karin; Karin 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 Karin and thus lower the plasma levels of Karin, while increasing those of 14-OH-Karin, a metabolite that is also microbiologically active. Since the microbiological activities of Karin and 14-OH-Karin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of Karin and enzyme inducers.

Etravirine
Karin exposure was decreased by etravirine; however, concentrations of the active metabolite, 14-OH-Karin, were increased. Because 14- OH-Karin has reduced activity against Mycobacterium avium complex (MAC), overall activity against this pathogen may be altered; therefore alternatives to Karin 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 steady-state minimum clarithromycin concentration (C_{min}) and area under the curve (AUC) of 33% and 18% respectively. Steady state concentrations of the active metabolite 14-OH-clarithromycin were not significantly affected by

concomitant administration of fluconazole. No Karin 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 C_{max} increased by 31%, C_{min} increased 182% and AUC increased by 77% with concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14-OH-clarithromycin 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 CL_{CR} 30 to 60 mL/min the dose of Karin should be reduced by 50%. For patients with CL_{CR}<30 mL/min the dose of Karin should be decreased by 75%. Doses of Karin 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 (see section below, Bi-directional drug interactions).

Ivabradine
Clarithromycin is considered to be a strong cytochrome P450 3A4 inhibitor which is the primary enzyme for Ivabradine metabolism. This may result in increased Ivabradine plasma exposure, hence concomitant administration of Karin and Ivabradine is contraindicated (see section 4.3).

Effect of Karin on other medicinal products
CYP3A-based interactions
Co-administration of Karin, known to inhibit CYP3A, and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant medicinal product. The use of Karin is contraindicated in patients receiving the CYP3A substrates astemizole cisapride,domperidone, pimozide and terfenadine due to the risk of QT prolongation and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation,and torsades de pointes (see sections 4.3 and 4.4). The use of Karin is also contraindicated with ergot alkaloids, oral midazolam, HMG CoA reductase inhibitors metabolised mainly by CYP3A4 (e.g. lovastatin and simvastatin), colchicine, ticagrelor, ivabradine and ranolazine (see section 4.3). Karin should be used with caution in patients receiving treatment with other drugs known to be CYP3A enzyme substrates, especially if the CYP3A substrate has a narrow safety margin (e.g. carbamazepine) and/or the substrate is extensively metabolized by this enzyme.

Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving Karin.

The following drugs or drug classes are known or suspected to be metabolized by the same CYP3A isozyme: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, ciclosporine, disopyramide, ergot alkaloids, ibrutinib, lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g. warfarin, rivaroxaban, apixaban, see section 4.4), atypical antipsychotics (e.g. quetiapine), pimozide, quinidine, rifabutin, sildenafil, simvastatin, sirolimus, tacrolimus, terfenadine, triazolam and vinblastine, but this list is not comprehensive. Drugs interacting by similar mechanisms through other isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

Direct acting oral anticoagulants (DOACs)
The DOACs dabigatran and edoxaban are a substrate for the efflux transporter P-gp. Rivaroxaban and apixaban are metabolised via CYP3A4 and are also substrates for P-gp. Caution should be exercised when Karin is co-administered with these agents particularly to patients at high risk of bleeding (see section 4.4).

Antiarrhythmics
There have been postmarketing reports of torsades de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QT prolongation during co-administration of Karin with these drugs. Serum levels of quinidine and disopyramide should be monitored during Karin therapy.

There have been post marketing reports of hypoglycemia with the concomitant administration of clarithromycin and disopyramide. Therefore blood glucose levels should be monitored during concomitant administration of Karin and disopyramide.

Oral hypoglycemic agents/Insulin
With certain hypoglycemic drugs such as nateglinide, and repaglinide, inhibition of CYP3A enzyme by Karin may be involved and could cause hypolgycemia when used concomitantly. Careful monitoring of glucose is recommended.

Omeprazole
Clarithromycin (500 mg every 8 hours) was given in combination with omeprazole (40 mg daily) to healthy adult subjects. The steady-state plasma concentrations of omeprazole were increased (C_{max}, AUC_{0-24}, and $t_{1/2}$ increased by 30%, 89%, and 34%, respectively), by the concomitant administration of clarithromycin. The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when omeprazole was co-administered with clarithromycin.

Sildenafil, tadalafil, and vardenafil
Each of these phosphodiesterase inhibitors is metabolized, at least in part, by CYP3A, and CYP3A may be inhibited by concomitantly administered Karin. Co-administration of Karin with sildenafil, tadalafil or vardenafil would likely result in increased phosphodiesterase inhibitor exposure. Reduction of sildenafil, tadalafil and vardenafil dosages should be considered when these drugs are co-administered with Karin.

Theophylline, carbamazepine
Results of clinical studies indicate there was a modest but statistically significant ($p \leq 0.05$) increase of circulating theophylline or carbamazepine levels when either of these drugs were administered concomitantly with clarithromycin. Dose reduction may need to be considered.

Tolterodine
The primary route of metabolism for tolterodine is via the 2D6 isoform of cytochrome P450 (CYP2D6). However, in a subset of the population devoid of CYP2D6, the identified pathway of metabolism is via CYP3A. In this population subset, inhibition of CYP3A results in significantly higher serum concentrations of tolterodine. A reduction in tolterodine dosage may be necessary in the presence of CYP3A inhibitors, such as clarithromycin in the CYP2D6 poor metabolizer population.

Triazolobenzodiazepines (e.g. alprazolam, midazolam, triazolam)
When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 2.7-fold after intravenous administration of midazolam and 7-fold after oral administration. Concomitant administration of oral midazolam and Karin should be avoided. If intravenous midazolam is co-administered with Karin, the patient must be closely monitored to allow dose adjustment. Active substance delivery of midazolam via oromucosal route, which could bypass pre-systemic elimination of the active substance, will likely result in a similar interaction to that observed after intravenous midazolam rather than oral administration. The same precautions should also apply to other benzodiazepines that are metabolized by CYP3A, including triazolam and alprazolam. For benzodiazepines which are not dependent on CYP3A for their elimination (temazepam, nitrazepam, lorazepam), a clinically important interaction with Karin is unlikely.

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.

Other drug interactions

Colchicine
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. (see section 4.3 and 4.4).

Corticosteroids
Caution should be exercised in concomitant use of Karin with systemic and inhaled corticosteroids that are primarily metabolised by CYP3A due to the potential for increased systemic exposure to corticosteroids. If concomitant use occurs, patients should be closely monitored for systemic corticosteroid undesirable effects.

Digoxin
Digoxin is thought to be a substrate for the efflux transporter, P-glycoprotein (Pgp). Clarithromycin is known to inhibit Pgp. When clarithromycin and digoxin are administered together, inhibition of Pgp by clarithromycin may lead to increased exposure to digoxin. Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have also been reported in post marketing surveillance. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Serum digoxin concentrations should be carefully monitored while patients are receiving digoxin and Karin simultaneously.

Zidovudine
Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. Because clarithromycin appears to interfere with the absorption of simultaneously administered oral zidovudine, this interaction can be largely avoided by staggering the doses of Karin and zidovudine to allow for a 4-hour interval between each medication. This interaction does not appear to occur in paediatric HIV-infected patients taking clarithromycin suspension with zidovudine or dideoxyinosine. This interaction is unlikely when clarithromycin is administered via intravenous infusion.

Phenytoin and Valproate
There have been spontaneous or published reports of interactions of CYP3A inhibitors, including clarithromycin with drugs not thought to be metabolized by CYP3A (e.g. phenytoin and valproate). Serum level determinations are recommended for these drugs when administered concomitantly with clarithromycin. Increased serum levels have been reported

For patients with moderate renal function (creatinine clearance 30 to 60 mL/min), the dose of Karin should be decreased by 50%. For patients with creatinine clearance <30 mL/min, the dose of Karin should be decreased by 75% using an appropriate Karin formulation. Doses of Karin greater than 1000 mg per day should not be co- administered with protease inhibitors.

Calcium Channel Blockers

Caution is advised regarding the concomitant administration of Karin and calcium channel blockers metabolized by CYP3A4 (e.g., verapamil, amlodipine, diltiazem) due to the risk of hypotension. Plasma concentrations of clarithromycin as well as calcium channel blockers may increase due to the interaction. Hypotension, bradyarrhythmias and lactic acidosis have been observed in patients taking clarithromycin and verapamil concomitantly.

Itraconazole

Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, leading to a bidirectional drug interaction. Karin may increase the plasma levels of itraconazole, while itraconazole may increase the plasma levels of Karin. Patients taking itraconazole and Karin concomitantly should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effect.

Saquinavir

Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Concomitant administration of clarithromycin (500 mg twice daily) and saquinavir (soft gelatin capsules, 1200 mg three times daily) to 12 healthy volunteers resulted in steady-state AUC and C_{max} values of saquinavir which were 177% and 187% higher than those seen with saquinavir alone. Clarithromycin AUC and C_{max} values were approximately 40% higher than those seen with clarithromycin alone. No dose adjustment is required when the two drugs are co-administered for a limited time at the doses/formulations studied. Observations from drug interaction studies using the soft gelatin capsule formulation may not be representative of the effects seen using the saquinavir hard gelatin capsule. Observations from drug interaction studies performed with saquinavir alone may not be representative of the effects seen with saquinavir/ritonavir therapy. When saquinavir is co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on Karin.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of clarithromycin for use during pregnancy has not been established. Based on variable results obtained from studies in mice, rats, rabbits and monkeys, the possibility of adverse effects on embryofoetal development cannot be excluded. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risk.

Breast-feeding

The safety of clarithromycin for use during breast feeding of infants has not been established. Clarithromycin is excreted into human breast milk.

Fertility

There is no data available on the effect of clarithromycin on fertility in humans. In the rat, fertility studies have not shown any evidence of harmful effects.

4.7 Effects on ability to drive and use machines

There are no data on the effect of clarithromycin on the ability to drive and use machines. Visual impairment and vision blurred may have an effect on a patient's ability to drive or operate machinery (see section 4.8). 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

a. Summary of the safety profile

The most frequent and common adverse reactions related to Karin therapy for both adult and pediatric populations are abdominal pain, diarrhea, nausea, vomiting and taste perversion. These adverse reactions are usually mild in intensity and are consistent with the known safety profile of macrolide antibiotics (see section b of section 4.8).

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

b. Tabulated summary of adverse reactions

The following table displays adverse reactions reported in clinical trials and from post-marketing experience with clarithromycin immediate-release tablets.

The reactions considered at least possibly related to Karin 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.

Infections and infestations

Uncommon: Cellulitis[1,] candidiasis, gastroenteritis[2], infection[3], vaginal infection

Not known: Pseudomembranous colitis, erysipelas

Blood and the lymphatic system disorders
Uncommon: Leukopenia, neutropenia[4], eosinophilia[4]
Not known: Agranulocytosis, thrombocytopenia
*Immune system disorders**
Uncommon: Anaphylactoid reaction[1], hypersensitivity
Not known: Anaphylactic reaction, angioedema

Metabolism and nutrition disorders
Uncommon: Anorexia, decreased appetite
Psychiatric disorders
Common: Insomnia
Uncommon: Anxiety, nervousness[3]
Not known: Psychotic disorder, confusional state[5], depersonalisation, depression, disorientation, hallucination, abnormal dreams, mania
Nervous system disorders
Common: Dysgeusia, headache, taste perversion
Uncommon: Loss of consciousness[1], dyskinesia[1], dizziness, somnolence[5], tremor
Not known*: Convulsion, ageusia, parosmia, anosmia , paraesthesia
Ear and labyrinth disorders
Uncommon: Vertigo, impaired hearing, tinnitus
Not known*: deafness
Cardiac disorders
Uncommon: Cardiac arrest[1], atrial fibrillation[1], electrocardiogram QT prolonged
Not known: Torsade de Pointes[*], ventricular tachycardia[*], ventricular fibrillation
Vascular disorders
Common: Vasodilation[1]
Not known*: Hemorrhage[#]
Respiratory, thoracic and mediastinal disorders
Uncommon: Asthma[1], epistaxis[2], pulmonary embolism[1]
Gastrointestinal disorders
Common: Diarrhea*, vomiting, abdominal pain, nausea, dyspepsia,
Uncommon: Oesophagitis[1], gastroesophageal reflux disease[2], gastritis, stomatitis, glossitis, abdominal distension[4], abdominal distension, constipation, dry mouth, eructation, flatulence,
Not known*: Pancreatitis, tongue discolouration, tooth discoloration
Hepato-biliary disorders
Common: Liver function test abnormal
Uncommon: Cholestasis[4], hepatitis[4], alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased[4]
Not known: Hepatic failure*, jaundice hepatocellular
Skin and subcutaneous tissue disorders
Common: Rash, hyperhidrosis
Uncommon: Dermatitis bullous[1,] pruritus, urticaria, rash maculo-papular[3]
Not known: Stevens-Johnson syndrome*, toxic epidermal necrolysis*, drug rash with eosinophilia and systemic symptoms (DRESS), acne, severe cutaneous adverse reactions (SCAR) (eg: acute generalised exanthematous pustulosis (AGEP)

Musculoskeletal, connective tissue and bone disorders
Uncommon: Muscle spasms[3], musculoskeletal stiffness[1], myalgia[2]
Not known*: Rhabdomyolysis[2,6], myopathy
Renal and urinary disorders
Uncommon: Blood creatinine increased[1], blood urea increased[1]
Not known: Renal failure, interstitial nephritis
General disorders and administration site conditions
Very common: Injection site phlebitis[1]
Common: Injection site pain[1], injection site inflammation[1]
Uncommon: Malaise[4], Pyrexia[3], asthenia, chest pain[4], chills[4], fatigue[4]

Investigations
Uncommon: Albumin globulin ratio abnormal[1], blood alkaline phosphatase increased[4], blood lactate dehydrogenase increased[4]
Not known: International normalised ratio increased[#], prolongation of prothrombin time[#], urine color abnormal

[1] ADRs reported only for the powder for solution for injection 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 Description of selected adverse reactions
* 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 medicinal product 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, vessel puncture 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 (see section 4.3 and 4.4).
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 (see section 4.5).
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 diarrhea. 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).

d. Paediatric populations

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. There are insufficient data to recommend a dosage regimen for use of the clarithromycin IV formulation in patients less than 18 years of age.

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 1,000 mg and 2,000 mg of clarithromycin were: nausea, vomiting, taste perversion, abdominal pain, diarrhea, 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 1,000 mg and 2,000 mg, but were generally about 3 to 4 times as frequent for those patients who received total daily doses of 4,000 mg 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 1,000 mg or 2,000 mg 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 4,000 mg daily for all parameters except White Blood Cell.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form.
http://forms.gov.il/globaldata/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9 Overdose

Reports indicate the ingestion of large amounts of Karin can be expected to produce gastrointestinal symptoms. One patient who had a history of bipolar disorder ingested eight grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalaemia and hypoxaemia.

Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed drug and supportive measures.

As with other macrolides, Karin serum levels are not expected to be appreciably affected by hemodialysis or peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
ATC Code J01FA09.

Clarithromycin is a semi-synthetic derivative of erythromycin A.

Mechanism of action:
Clarithromycin 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.

Breakpoints

	NCCLS*		BSAC**	
	susceptible (µg/ml)	resistant (µg/ml)	susceptible (µg/ml)	resistant (µg/ml)
Staphylococcus spp.	≤ 2	≥ 8	≤ 0.5	≥ 1
Haemophilus spp.	≤ 8	≥ 32	≤ 0.5	≥ 32
Streptococcus pneumoniae	≤ 0.25	≥ 1	≤ 0.5	≥ 1
Streptococcus spp. other than S. pneumoniae	≤ 0.25	≥ 1	≤ 0.5	≥ 1
Helicobacter pylori	≤ 0.25	≥ 1	≤ 1	≥ 2

* National Committee on Clinical Laboratory Standards, in 2001
** British Society for Antimicrobial Chemotherapy

Susceptibility
The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly

when treating severe infections. This information gives only an appropriate guidance on the probabilities whether micro-organisms will be susceptible to clarithromycin or not. As far as applicable the information on the European range of acquired resistance for the individual micro-organism is indicated in brackets.

Species	Frequency of resistance ranges in EU (if > 10%) (extreme values)[1)]
Susceptible	
Gram-positive aerobes	
Staphylococcus aureus (methicillin-susceptible)	(18.1%)
Streptococcus pyogenes	
Streptococcus agalactiae	
Group C, F, G Streptococci	
Streptococcus pneumoniae	(37.8%)
Gram-negative aerobes	
Haemophilus infuenzae	(13.4%)
Helicobacter pylori	(14%)
Legionalla spp.	
Moraxella catarrhalis	
Neisseria gonorrhoeae	
Anaerobes	
Bacteroides spp.	
Clostridum spp. other than C. difficile	
Fusobacterium spp.	
Peptococcus/Peptostreptococcus spp.	
Others	
Chlamydia trachomatis	
Chlamydia pneumoniae	
Mycoplasma pneumoniae	
Insusceptible	
Gram-positive aerobes	
Enterococcus spp.	
Staphylococcus aureus (Erythromycin resistant or MRSA)	
Others	
Mycobacterium tuberculosis	

MRSA - methicillin resistant *Staphylococcus aureus*

[1)] Frequencies of resistance ranges calculated on NCCLS breakpoints

Other information

Susceptibility and resistance of *Streptococcus pneumoniae* and *Streptococcus* spp. to clarithromycin can be predicted by testing erythromycin.

The mechanisms of acquired resistance in macrolides are: efflux of drug by an active pump mechanism, inducible or constitutive production of a methylase enzyme that modifies the ribosomal target, hydrolysis of macrolides by esterases, chromosomal mutations that alter a 50 S ribosomal protein. Cross-resistance between clarithromycin and other macrolides and clindamycin and

lincomycin may therefore occur. Methicillin-resistant and oxacillin-resistant staphylococci (MRSA) and penicillin-resistant Streptococcus pneumoniae are resistant to all currently available Beta-lactam antibiotics and macrolides such as clarithromycin.

Most available clinical experience from controlled randomised clinical trials indicate that clarithromycin 500 mg twice daily in combination with another antibiotic e.g. amoxicillin or metronidazole e.g. omeprazole (given at approved levels) for 7 days achieve > 80% H. pylori eradication rate in patients with gastro-duodenal ulcers. As expected, significantly lower eradication rates were observed in patients with baseline metronidazole-resistant H. pylori isolates. Hence, local information on the prevalence of resistance and local therapeutic guidelines should be taken into account in the choice of an appropriate combination regimen for H. pylori eradication therapy. Furthermore, in patients with persistent infection, potential development of secondary resistance (in patients with primary susceptible strains) to an antimicrobial agent should be taken into the considerations for a new treatment regimen.

5.2 Pharmacokinetic properties

Absorption:
Clarithromycin is rapidly and well absorbed from the gastrointestinal tract – primarily in the jejunum - after oral administration. Due to its chemical structure (6-O-Methylerythromycin) clarithromycin is quite resistant to degradation by stomach acid. Serum levels of 1 – 2 µg/ml clarithromycin were observed in adults after oral administration of 250 mg twice daily. After administration of 500 mg clarithromycin twice daily serum levels of 2,8 µg/ml were obtained.

After administration of 250 mg clarithromycin twice daily the pharmacological active 14-hydroxy metabolite attains peak plasma concentrations of 0,6 µg/ml.

Distribution:
Clarithromycin gives good penetration into different compartments. Therapeutic drug levels exceeding the minimum inhibitory levels for common pathogens can be rapidly achieved. 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 also penetrates the gastric mucus.

Clarithromycin is 80% bound to plasma proteins at therapeutic levels.

Serum half-life:
The serum half-life of the active 14-(R)-hydroxy metabolite ranges between 5 to 6 hours.

Biotransformation and elimination:
Clarithromycin is rapidly and extensively metabolised in the liver. Metabolism involves mainly N-dealkylation, oxidation and stereospecific hydroxylation at position C 14.

After oral administration of radioactive clarithromycin 70 - 80% of the radioactivity was found in the faeces. Approximately 20 -30% of clarithromycin is collected as the unchanged parent molecule in the urine. This proportion is increased when the dose is increased. Renal insufficiency increases clarithromycin levels in plasma, if the dose is not decreased.

The pharmacokinetics of clarithromycin are non linear. This is an indication for a saturation of hepatic metabolism at high doses; however, steady state is attained within 2 days of dosing.

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).

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 Spraque-Dawley (p.o. and i.v.)), New Zealand White rabbits and cynomolgus monkeys failed to demonstrate any teratogenicity from clarithromycin. However, a further similar study in Sprague-Dawley rates 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 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, Pregelatinized starch, Carmellose sodium LS, Povidone, Glyceryl behenate, Magnesium stearate, Colloidal silicon dioxide, Opadry OY-6900.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packing materials.

6.4 Special precautions for storage

Karin coated tablets should be stored at a temperature below 25ºC and in a place protected from light.

6.5 Nature and contents of container

- Packed in PVC aluminium blister

- Pack sizes:

Karin 250: 2, 10, 14, 20, 28.

Karin 500: 1, 2, 7, 10, 14, 21, 28.

- Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Unipharm Ltd. P.O.B. 16545, Tel-Aviv 6116401.

Manufacturer: Unipharm Ltd. - "Mevo Carmel" Industrial Park.

8 MARKETING AUTHORISATION NUMBER(S)

Karin 250: **104-96-28719-01**
Karin 500: **109-30-29343-01**

9 DATE OF REVISION OF THE TEXT

Revised in December 2024.