Special warnings and special precautions for use

Warnings
- Cases of pseudomembranous enterocolitis have been observed with practically all anti-infectious agents, including macrolides. They may be moderately severe or life-threatening.
- When treating infections due to Mycobacterium avium in HIV-infected patients, and in order to limit the emergence of resistant strains, clarithromycin must be used:
  - in combination with other antibiotics and not as single-agent therapy,
  - only for curative purposes, also because there are no studies on prophylactic use.
- Do not combine with other ototoxic medicinal products, particularly aminoglycosides.
- Concomitant administration of clarithromycin and any of the following is inadvisable: dopaminergic ergot alkaloids, alfuzosin, colchicine, ebastine, halofantrine, lumefantrine, tolterodine and tacrolimus.

Precautions for use
- An audiogram should be carried out and changes in the dose envisaged if tinnitus or reduced auditory acuity occurs.
- Do not administer other products in the vein receiving the IV infusion.
- In patients with severe hepatic insufficiency, the administration of clarithromycin is not recommended. If it is necessary, regular monitoring of liver function tests is required.
- In patients with moderate or severe renal insufficiency (creatinine clearance less than 30 ml/minute), the prolongation in half-life requires either a greater interval between doses or a reduction in the dosage
- In elderly subjects, prolongation of the half-life and the increase in the areas under the curves for the plasma concentrations do not theoretically imply particular monitoring, in view of the treatment duration (cf. section on excretion).
- The possible cross-resistance between clarithromycin and other macrolides, and other antibiotics, such as lincomycin and clindamycin should be taken into account.

**Interaction with other medicinal products and other forms of interaction**

**Contraindicated combinations**
- Bepridil: increased risk of ventricular rhythm disorders, including torsades de pointes.
- Cisapride: increased risk of ventricular rhythm disorders, including torsades de pointes.
- Dihydroergotamine: ergotism with possible necrosis of the extremities (reduced hepatic elimination of ergotalkaloids)
- Ergotamine: ergotism with possible necrosis of the extremities (reduced hepatic elimination of ergotamine).
- Mizolastine: risk of ventricular rhythm disorders, including torsades de pointes.
- Pimozide: increased risk of ventricular rhythm disorders, including torsades de pointes.
- Simvastatin: increased risk of undesirable effects (concentration-dependent), such as rhabdomyolysis (reduced hepatic metabolism of the cholesterol-lowering drug).

**Inadvisable combinations**
- Dopaminergic ergot alkaloids (bromocriptine, cabergoline, lisuride, pergolide): increased plasma concentrations of the dopaminergic agent with possible increase in activity or appearance of symptoms of overdose.
- Alfuzosine: risk of increased plasma concentrations of alfuzosine and of increased undesirable effects.
- Colchicine: increase of the undesirable effects of colchicine with a potentially fatal outcome.
- Ebastine: increased risk of ventricular rhythm disorders in predisposed subjects (congenital, long QT syndrome).
- Halofantrine: increased risk of ventricular rhythm disorders, including torsades de pointes. If possible, the macrolide should be discontinued. If the combination cannot be avoided, the QT interval should be controlled beforehand and the ECG monitored.

- Lumefantrine: increased risk of ventricular rhythm disorders, including torsades de pointes. If possible, the agent inducing torsades de pointes should be discontinued. If the combination cannot be avoided, the QT interval should be controlled beforehand and the ECG monitored.

- Tacrolimus: elevated blood concentrations of tacrolimus and blood creatinine through inhibition of the hepatic metabolism of tacrolimus by clarithromycin.
- Tolterodine: increased tolterodine plasma concentrations in slow metabolizers, with a risk of overdose.

**Combinations requiring precautions for use**
- Oral anticoagulants: increase in the oral anticoagulant effect and in the risk of hemorrhage. More frequent monitoring of INR. Dosage of the oral anticoagulant may be adjusted, during treatment with the macrolide and after treatment discontinuation.
- Atazanavir: elevated plasma clarithromycin concentrations and inhibition of the formation of its active metabolite. Regular clinical and laboratory monitoring, particularly at the start of combination therapy.
- Atorvastatin: increased risk of undesirable effects (concentration-dependent), such as rhabdomyolysis (reduced hepatic metabolism of the cholesterol-lowering drug). Use lower doses of the cholesterol-lowering agent. If the therapeutic objective is not achieved, use another statin not affected by this type of interaction.
- Carbamazepine: elevated plasma carbamazepine concentrations with signs of overdose, through the inhibition of its hepatic metabolism. Clinical surveillance and possible reduction in the carbamazepine dosage.

- Ciclosporin: risk of elevated blood concentrations of ciclosporin and blood creatinine. Assay of blood ciclosporin concentrations, checks on the renal function and adjustment of the dosage during the combination and after its discontinuation.
- Digoxin: elevated blood digoxin levels through an increase in its absorption. Monitoring of clinical parameters and if necessary of blood digoxin levels during treatment with clarithromycin and after its discontinuation.
Pregnancy and lactation

Pregnancy
As a precautionary measure, clarithromycin should preferably not be used during pregnancy. The clinical data on a limited number of pregnancies are reassuring; however, studies in the mouse have evidenced a teratogenic effect (cleft palate) at a dose of 1000 mg/kg. Prenatal surveillance may be envisaged in case of exposure during the first trimester of pregnancy.

Lactation
Although no data are available concerning the excretion of clarithromycin into breast-milk, the fact that those macrolides which have been studied have been shown to pass into breast-milk suggests that excretion of clarithromycin into breast-milk cannot be excluded. Breast-feeding is possible in case of intake of clarithromycin; however, breast-feeding (or the medicinal product) should be discontinued if gastrointestinal disorders occur in the neonate.

Administration of clarithromycin to mothers of neonates or breast-fed infants receiving cisapride is contraindicated as a precautionary measure owing to the potential risk of interaction in the infant (torsades de pointes).

Effects on ability to drive and use machines
Not applicable.

Undesirable effects
- Gastrointestinal disorders: nausea, vomiting, gastric pain, diarrhea.
- Oral candidiasis, glossitis, stomatitis.
- Allergic skin reactions: bullous skin reactions, including exceptional cases of erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported.
- Transient elevation in AST-ALT levels which can, in exceptional cases, lead to cholestatic hepatitis.
- Cases of tinnitus and hypoacusis, generally reversible, as a rule, on stopping treatment, have been reported at doses of 1 g/day or above 1 g/day over prolonged treatment periods.
- Rare cases of dysgeusia have been reported.

Combinations to be taken into account
- Disopyramide: risk of onset of severe hypoglycemia, through the inhibition of disopyramide metabolism by clarithromycin. Regular clinical and laboratory monitoring.
- Phosphodiesterase type 5 inhibitors (sildenafil, tadalafil except vardenafil): increased plasma concentrations of the PDE5 inhibitor, with a risk of hypotension. Treatment with the PDE5 inhibitor should be initiated at the minimum dose.
- Midazolam: elevated plasma midazolam concentrations through a reduction in its hepatic metabolism, with increased sedation. Clinical surveillance and reduction of the midazolam dosage during treatment with clarithromycin.
- Pravastatin: elevated plasma pravastatin concentrations by clarithromycin. Clinical and laboratory monitoring during treatment with the antibiotic.
- Rifabutin: risk of increased undesirable effects with rifabutin (uveitis) through an elevation of its concentration and that of its active metabolite by clarithromycin. Moreover, accelerated metabolism of clarithromycin by rifabutin, with increased concentrations of its active metabolite. Regular clinical and laboratory monitoring, particularly at the start of combination therapy.
- Ritonavir: elevated plasma clarithromycin concentrations and that of its active metabolite by the inhibition of its hepatic metabolism by ritonavir. Regular clinical and laboratory monitoring, particularly at the start of combination therapy.
- Triazolam: elevated plasma triazolam concentrations through a reduction in its hepatic metabolism, with increased sedation. Clinical surveillance and reduction of the triazolam dosage during treatment with clarithromycin.
- Vardenafil: major increase in plasma vardenafil concentrations with a risk of severe hypotension. Reduction in vardenafil dose.

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Theophylline (and, by extrapolation, aminophylline):
- risk of elevation of plasma theophylline concentrations, particularly in children.
- Zolpidem: slight increase in the sedative effects of zolpidem.
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- Although no links have been officially established, cases of dental discoloration, usually reversible with dental treatment, have been reported.
- Inflammation at the injection site has been frequently observed.
- Cases of interstitial nephritis have been reported, consistent with the use of clarithromycin.

**Overdose**
Actions to be taken in the event of an overdose: symptomatic treatment.

**PHARMACOLOGICAL PROPERTIES**

**Pharmacodynamic properties**
Clarithromycin is a semi-synthetic bacterial antibiotic derived from erythromycin A, belonging to the macrolide group (in C14).

**SPECTRUM OF ANTIMICROBIAL ACTIVITY:**
The critical concentrations differentiating susceptible strains from intermediate strains and the latter from resistant strains are as follows: S ≤1 mg/l and R >4 mg/l. The prevalence of acquired resistance in certain species can vary geographically and over time. It is therefore useful to have local information on resistance, especially in treating severe infections. These data are only guidelines indicating the probability of susceptibility of a bacterial strain to this antibiotic. When the variability of prevalence of resistance of a bacterial species is known in France, it is indicated below: Category [Incidence of acquired resistance in France (>10%) (range)]:

**SUSCEPTIBLE SPECIES:** Gram-positive aerobic: Bacillus cereus, Corynebacterium diphtheriae, Enterococci [50-70%], Lactobacillus, Rhodococcus equi, Staphylococcus meti-S, Staphylococcus meti-R* [70-80%], Streptococcus B, unclassified streptococcus [30-40%], Streptococcus pneumoniae [35-70%], Streptococcus pyogenes [16-31%].

**MODERATELY SUSCEPTIBLE SPECIES** (intermediate susceptibility *in vitro*)

**RESISTANT SPECIES:** Gram-positive aerobic:

- Corynebacterium jeikeium, Nocardia asteroides.
- Anaerobic:
  - Fusobacterium, Leptotrichia. Miscellaneous: Mycoplasma hominis.

Clarithromycin has *in vitro* and *in vivo* activity on *Toxoplasma gondii*.

* The incidence of methicillin resistance is approximately 30 to 50% for all staphylococci, and is mainly found in the hospital setting.

**Haemophilus influenzae**: the activity of 14-hydroxy clarithromycin is greater than that of clarithromycin. *In vitro* studies have suggested an additive activity of 14-hydroxy clarithromycin and the parent compound against *Haemophilus influenzae*.

**PHARMACOKINETIC PROPERTIES**

**IV route.**
During studies with clarithromycin IV in healthy volunteers, doses of 75, 125, 250 and 500 mg in 100 ml were infused for 30 minutes, and doses of 500, 750 and 1000 mg in 250 ml for 60 minutes. The mean peak concentration (C max) is 1.23 μg/ml with 75 mg, and 9.40 μg/ml with 1000 mg. The C max of 14-hydroxy clarithromycin is 0.21 μg/ml with 125 mg, and 1.06 μg/ml with 1000 mg. The quantities of this metabolite cannot be detected below a dose of 75 mg. The elimination half-life of clarithromycin is dose-dependent. It lies between 2.1 hours after 75 mg and 4.5 hours after 1000 mg. The estimated mean plasma half-life of the 14-hydroxy metabolite shows a slight dose-dependent increase at high doses and ranges from 5.3 hours for 250 mg and 9.3 hours for 1000 mg. The estimated mean plasma half-life after 30 minutes of infusion at a dose of 125 mg is 7.2 hours. The mean AUC shows a non-linear dose-dependent increase for clarithromycin of 2.29 μgh/ml after 75 mg to 53.26 μgh/ml after 1000 mg. The mean AUC for 14-hydroxy clar-
ithromycin ranges from 2.10 μg/ml after 125 mg to 14.76 μg/ml after 1000 mg. In a 7-day multidose clinical study, the subjects received 125 and 250 mg of clarithromycin IV in a volume of 100 ml, infused over 30 minutes, or 500 to 750 mg in a volume of 250 ml over 60 minutes. Administration was carried out every 12 hours. In this study, the $C_{\text{max}}$ values increase from 2.1 μg/ml for 125 mg to 3.2, 5.5, 8.6 μg/ml for 250, 500 and 750 mg, respectively. The elimination half-life gradually increases from 2.8 hours after infusion of 125 mg to 6.3 hours for 500 mg. This is 4.8 hours for 750 mg. The $C_{\text{max}}$ at the steady state for the 14-hydroxyl metabolite increases from 0.33 μg/ml for 125 mg to 0.55, 1.02 and 1.37 μg/ml for doses of 250, 500 and 750 mg, respectively. The elimination half-lives for the metabolite are 4.8, 5.4, 7.9 and 5.4 hours for 125, 250, 500 and 750 mg, respectively. No dose relationship has been demonstrated.

Protein binding: The percentage serum protein binding for clarithromycin ranges from 72 to 67%, and that for the active metabolite is 57 to 48% as a function of plasma concentrations.

Tissue distribution: The volume of distribution is approximately 2 to 4 l/kg. After 5 doses of 250 mg, concentrations of 8.8 μg/ml are reached in the lungs, 1.11 μg/ml in the tonsils and approximately 0.9 μg/ml in the interstitial fluid. Macrolides enter and accumulate in phagocytes (PMN cells, monocytes, peritoneal and alveolar macrophages). The intraphagocytic concentrations are high in humans. These properties explain the activity of clarithromycin on intracellular bacteria. Clarithromycin and 14-OH clarithromycin are excreted into breast-milk. The ratio of the concentrations to plasma levels are 24 and 63%, respectively.

Biotransformation: Clarithromycin undergoes biotransformation into 3 metabolites: descladinosyl-clarithromycin, N-demethyl-clarithromycin and the 14-hydroxy derivative. The latter metabolite is predominant both in quantitative and qualitative terms since it is endowed with a specific antibacterial activity. Clarithromycin metabolism is saturable at high doses. Increasing the doses and the number of intakes gives rise to an increase in plasma clarithromycin concentrations proportionally higher than that of the doses and a reduction in the 14-OH clarithromycin fraction (at the steady state, the plasma concentrations of 14-OH clarithromycin are approximately 2/3 those of the parent molecule after 250 mg x 2, and approximately 27% after 500 mg x 2, cf.: Distribution).

Excretion: Clarithromycin is excreted by the liver and kidney.

- in humans, after a single dose of 250 mg PO, 37.9% of the dose is excreted in the urine, including 18.4% as clarithromycin, and 13.7% as the 14-hydroxyl derivative. Irrespective of the dose, free clarithromycin and the 14-hydroxyl derivative account for the majority of clarithromycin excretion in the urine.

- fecal elimination of a single 250-mg dose corresponds to 40.2%, with the parent molecule representing 4.4% of the dose. The majority of clarithromycin is eliminated in metabolite form.

- Increasing the doses increases urinary elimination together with the fraction of unchanged clarithromycin.

In the event of renal insufficiency, the excretion of clarithromycin, and 14-OH clarithromycin in particular, is reduced with an elevation in peak concentrations, residual concentrations, AUC and the quantity of 14-OH clarithromycin formed. When clearance is less than 30 ml/minute, the elimination half-life is increased threefold for clarithromycin and fourfold for 14-OH clarithromycin with a major risk of accumulation.

In the event of hepatic insufficiency, the formation of 14-OH clarithromycin is reduced, together with its serum concentrations and AUC. However, there is an increase in the renal elimination of clarithromycin, and no accumulation.

In elderly subjects (>65 years), there is an increase in $C_{\text{max}}$ and residual concentrations related to prolongation of the half-life of clarithromycin (>7.7 hours), particularly the 14-hydroxyl metabolite (14 hours). The AUCs for the plasma clarithromycin concentrations are double those observed in young adult subjects.
PHARMACEUTICAL PARTICULARS

Incompatibilities
Due to the lack of data, it is advisable to administer clarithromycin IV alone.

Special precautions for storage
Store at room temperature below 30°C.
Protect from light.
The initial solution after reconstitution (500 mg in 10 ml of water for injections) may be stored for 24 hours between 2 and 8°C (in the refrigerator).
The final solution after dilution (500 mg in 250 ml) may be stored for 24 hours between 2 and 8°C (in the refrigerator) or for 6 hours at a temperature below 25°C.

How supplied
Klacid IV lyophilized powder for injection is supplied in clear glass vials containing 500 mg of Clarithromycin.

Instructions for use and handling
Prepare the initial clarithromycin solution by adding 10 ml of water for injections to the contents of the vial containing clarithromycin 500 mg. The final solution is obtained by diluting the initial solution (500 mg in 10 ml of water for injections) in 250 ml of the following solutions: isotonic saline solution, 5% dextrose solution, Ringer’s lactate solution. The final solution is to be administered in 60 minutes.

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