Gasec™ 10, Gastrocaps™ (gastro-resistant capsule)

Gasec™ 20, Gastrocaps™ (gastro-resistant capsule)

Gasec™ 40, Gastrocaps™ (gastro-resistant capsule)

Qualitative and Quantitative composition
Each *Gastrocaps™* (gastro-resistant capsule) contains 10mg, 20mg or 40 mg of Omeprazol, respectively it is **Gasec™ 10, Gasec™ 20** or **Gasec™ 40**.
Excipients

Pharmaceutical form
Gasec™ 10, *Gastrocaps™* (gastro-resistant capsule): package with 14 and 28 gastro-resistant capsules, containing 10mg of Omeprazol.

Gasec™ 20, *Gastrocaps™* (gastro-resistant capsules): package with 14, 28 and 56 gastro-resistant capsules, containing 20mg of Omeprazol.

Gasec™ 40, *Gastrocaps™* (gastro-resistant capsules): package with 14 and 28 gastro-resistant capsules, containing 40mg of Omeprazol.

Clinical Particulars

Therapeutic Indications
- Duodenal ulcer.
- Benign gastric ulcers.
- Reflux esophagitis.
- Reflux esophagitis maintenance treatment for relapse prevention.
- Zollinger-Ellison Syndrome.
- Treatment of gastric and duodenal ulcers related with NSAID's.
- Maintenance treatment of the gastric and duodenal ulcers related with NSAID's for relapse prevention.
- Symptomatic treatment of the gastro reflux esophagitis disease.
- In association with antibacterial therapeutic regimens adequate for H. pylori eradication in patients with H. pylori associated to peptic ulcer (see section Posology and Method of Administration).

Posology and Method of Administration
Duodenal Ulcers:
The usual dose is 20 mg per day. The treatment duration is 2 - 4 weeks.
Benign gastric ulcer:
The usual dose is 20 mg once a day. The treatment duration is 4 - 8 weeks.
Reflux Esophagitis
The usual dose is 20 mg once a day. The treatment duration is 4 - 8 weeks.
Notes:
In isolated cases of, duodenal ulcers, benign gastric ulcers and gastro-esophagic reflux the omeprazol posology can be increased to 40 mg of Omeprazol once a day.
Monotherapy only with Omeprazol in duodenal and gastric ulcers can only be used in patients in whom the eradication treatment is not indicated.
Children above 2 years with acute reflux esophagitis:
The clinical experience in children is limited.
Omeprazol should only be used in children with acute reflux esophagitis resistant to other treatments.
The treatment should be started at a paediatric hospital.
The continuous pH measurement and the determination of the genotype (related to the CYP 2C19 situation) can be used and appropriated for an optimal therapeutic response.
The following doses should be used:
Weight 10kg to 20 kg: 10 mg/day
Weight above 20 kg: 20 mg/day (approximately 1 mg/kg/day).
The treatment duration is generally of 4 to 8 weeks and should not exceed the 12 weeks due to lack of data in the long term usage in this age group.
Reflux esophagitis maintenance treatment for the relapse prevention:
The usual dose is 10 mg to 20 mg depending on the clinic response.
Zollinger-Ellison Syndrome:
Posology should be adjusted to each individual and followed by specialist supervision while clinically indicated. The recommended initial dose is 60 mg once a day. Above 80 mg per day, the dose should be divided and taken twice a day. In patients with Zollinger-Ellison syndrome the treatment has no limited duration.
Treatment of gastric and duodenal ulcers related with NSAID's.
The usual dose is 20 mg per day. The treatment duration is 4 – 8 weeks.
Maintenance treatment of the gastric and duodenal ulcers related with NSAID's for the relapse prevention.
The usual dose is 20 mg per day.
Symptomatic treatment of gastro reflux esophagitis disease.
The usual dose is 10 mg to 20 mg once a day depending of the clinical response. The treatment duration is 2 to 4 weeks.
If the patient does not show any symptoms recovery after 2 weeks of treatment, more exams should be performed.
Eradication treatment:
Patients with gastro duodenal ulcers due to infection by *H. pylori* should be treated with eradication treatment with appropriate antibiotic associations in adequate posology regimens. The adequate regimen selection should be based in the patient tolerability and in the treatment guidelines. The following associations were tested:
- Omeprazol 20 mg, Amoxicillin 1000 mg, Clarithromycin 500 mg, all twice a day.
- Omeprazol 20 mg, Clarithromycin 250 mg, Metronidazol 400 - 500 mg, all twice a day.

The eradication treatment duration is 1 week. To avoid resistances development the duration should not be reduced.
In patients with gastric ulcers the treatment can be extended by the usage of monotherapy with Omeprazol according to the prescribed posology and treatment duration.

The association treatment with metronidazol should not be the first choice due to the suspect from animal studies that metronidazol can be mutagenic and carcinogenic.
Elderly:
It is not necessary to adjust the dose in elderly patients.
Renal failure:
It is not necessary to adjust the dose in renal failure patients.
Hepatic failure:
Biodisponibility and the half-life can be increased in patients with hepatic failure,therefore is mandatory to adjust the dose with a daily maximum dose of 20 mg.

The gastro-resistant capsules should be swallowed intact with enough liquid (for example 1 glass of water) before meals (example, before breakfast or dinner).

Contra-Indications
Omeprazol is contra-indicated in patients with known hypersensitivity to Omeprazol or to other formulation compound.
The association treatment with clarithromycin should not be used in patients with hepatic failure.

Special Warnings and precautions for Use
If relevant in patients with peptic ulcer, it should be determined the *status Helicobacter pylori*. In patients *Helicobacter pylori* positive, should always be done the microorganisms elimination by the eradication treatment.
If there is a suspect of gastric ulcer, it should be excluded the possibility of malignance before Gasec™ 10/ 20/ 40 treatment (Omeprazol 10/ 20/ 40 mg) be started. As treatment can relieve symptoms and delay diagnosis.
The reflux esophagitis diagnosis should be confirmed by endoscopy.
The reduction in gastric acid by any means – including proton pump inhibitor – increases the gastric bacterial counting normally present in the gastrointestinal tract. The treatment with drugs that reduce the gastric acid lead to a slight increase in the gastrointestinal infections, such as those caused by *Salmonella* and *Campylobacter*.
Omeprazol should be used with caution in elderly patients and in renal and hepatic failure patients, specially in high doses. In patients with acute hepatic failure the maximum daily dose should be 20 mg.
During the treatment with Gasec™ 10/ 20/ 40 (Omeprazol 10/ 20/ 40 mg), in acute hepatic failure patients, the hepatic enzyme values should be controlled regularly.
This drug contains saccharose. Patients with rare hereditary problems of intolerance to fructose, bad glucose absorption -galactose or insufficiency in saccharase-isomaltase, should not take this drug.
Before starting the treatment of NSAID's related ulcers, it should be considered the possibility of interrupting the causative agent ingestion.
The maintenance treatment of gastric ulcers associated to ingestion of non steroid anti-inflammatory drugs should be restricted to patients at risk.
In the long-term use, especially after 1 year, the doctor should perform a regular treatment evaluation and a periodic evaluation of benefit-risk relation.
During Omeprazol treatment in cases where the administration of associated drugs is required (ulcers related with NSAID's or eradication) extra care should be taken when other drugs are added because it cause the appearance or potenciation of interactions increase (see other drugs SPC's)
Caution should be taken during association treatment in patients with renal or hepatic failure.
The Omeprazol should not be used in babies or children under 2 years old.
In patients with a severe condition it is recommended that sight and hearing senses should be monitorised because there were isolated cases of blindness and deafness with the regular use of injectable Omeprazol.

Interaction with other Medicines and others
Omeprazol is mainly metabolised by the isoforms of P-450 cytochrome (mainly CYP2C19, S-mephenitoin hydroxilase) and inhibit the subfamily enzymes CYP2C (CYP2C19 and CYP2C9). Omeprazol can delay the elimination of other drugs metabolised by this enzymes.
This was observed for diazepam (and also with other benzodiazepines such has triazolam or flurazepam), phenytoin and warfarin. It is recommended the periodic monitorisation of patients taking warfarin or phenitoin, and could be necessary to reduce the dose of this substances. Other drugs that can affect are hexabarbital, citalopram, imipramine, clomipramine etc.

Omeprazol can inhibit the hepatic metabolism of disulfiram. There were some reported isolated and probably related cases of muscle rigidity.

There are contradictory data about Omeprazol interaction with cyclosporine. Therefore cyclosporine plasma levels should be monitorised in patients taking Omeprazol, becauseit is possible an increase in the cyclosporin levels.

There is an increase in Omeprazol and clarithromycin plasma concentrations during the concomitant administration.

Due to the decrease in intra-gastric acidity, the ketoconazol or itraconazol absorption can be decreased during treatment with Omeprazol like with other acid secretion inhibitors.

Simultaneous treatment with Omeprazol and digoxin in healthy individuals lead into an increase of 10 % in digoxin biddisponibility as consequence of an increase in gastric pH.

Omeprazol can decrease vitamin B12 oral absorption of. This should be taken in consideration in patients with low baseline levels that are under long-term therapeutic with Omeprazol.

There is no evidence of Omeprazol interaction with caffeine, propranolol, theophylline, metoprolol, lidocaine, quinidine, fenacetine, estradiol, amoxicillin, budesonide, diclofenac, metronidazol, naproxen, piroxicam, or antiacids. Omeprazol absorption is not affected by alcohol.

Table with Omeprazol major interactions

Other drugs	Cause	Resultant effect
Diazepem (and probably another benzodiazepines) R-warfarin Fenitoin	Interactions with metabolized enzyme CYP 2C of cytochrome 450	Increase in elimination period, increase in plasma levels.
Ketoconazole Itraconazole (and other drugs with absorption pH-dependent)	Increase in gastric pH	Reduced absorption
Digoxin	Increase in gastric pH	Biodisponibility increase in 10 %
Clarithromycin Roxitromycin Eritromycinin (and probably other macrolide as well)	Changes in gastric pH and in hepatic metabolite	High plasma concentrations; increase biodisponibility and Omeprazol half life
Alcohol Amoxicilin Budesonide Quinidine Caffeine Diclofenac Estradiol Lidocaine Metoprolol Metronidazol Naproxen Fenacetine Piroxicam Propranolol S-Warfarin Teophylline		There are no pharmacokinetics alterations

Pregnancy and Lactation

Epidemiological studies do not indicate adverse effects during pregnancy or increase in malformations rate, in general. However, there is no information respecting specific abnormalities.

In rats, Omeprazol and is metabolites are excreted to milk. There is no sufficient data about the baby's exposition by lactation route. Omeprazol concentration in the human mother's milk reaches around 6 % of the mother maximum plasma concentration.

The use of Omeprazol during pregnancy and lactation requires a careful evaluation of the benefit-risk.

Effects on Ability to drive and use machines

There are no studies about the ability to drive with concomitant Omeprazol ingestion. However, except in rare and very rare cases of side effects affecting the CNS or the visual abilities, effects are not expected in the driving capability with Omeprazol administration.

Undesirable effects

Gastrointestinal Disturbances
Common (10% - 1%):
Diarrhea, obstipation, flatulence (possibly with abdominal pain), nauseas and vomits. In the majority of these cases the symptoms recover if the treatment continues.
Rare (0,1% - 0,01%):
It was observed a brown-black coloration in the longue, during the clarithromycin concomitant administration and glandular benign cyst; both were reversible with the treatment conclusion.
Very rare (<0,01%):
Mouth dryness, stomatitis, candidiase or panchreatits.

Hepato-biliary disturbances
Little commons (1% - 0,1%):
Changes in the hepatic enzymes values (resolved after treatment interruption).
Very rare (<0,01%):
Hepatitis with or without icterus, hepatic failure and encephalopathy in patients with serious pre-existing hepatic disease.

Blood and lymphatic system disturbances
Very rare (0,01%):
Alterations in blood count, reverse thrombocytopenia, leucopenia or pancytopenia and agranulocytosis.
Rare (0,1 % - 0,01 %):
Inadequate pigmentation (Hypocromia), microcitic anaemia in children.

Skin and subcutaneous tissues
Less commons (1% - 0,1%):
Pruritus skin eruption, alopecia, multiform erythema or fotosensitivity and increased tendency for sudation.
Very rare (>0,01%):
Stevens-Johnson Syndrome or toxic epidermal necrosis.

Muscle-skeletal disturbances
Rare (0,1% - 0,01%):
Muscle weakness, mialgia and join pain.

Renal disturbances
Very rare (<0,01%):
Nephritis (interstitial nephritis).

Nervous system disturbances
Common (1% - 10%):
Somnolence, sleeping disturbances (insomnia), vertigo and migraine. This complaints in general improve during treatment continuation.
Rare (0,1% - 0,01 %):
Paresthesia, and slight headache. Mental confusion, hallucination mainly in individuals seriously ill and elderly.
Very rare (<0,01%):
Agitation and depressive reactions mainly in individual seriously ill and elderly.

Sensorial organs disturbances
Little commons (1% - 0,1%):
Vision disorder (blurred vision, visual acuity loss or visual field reduction) and auditive dysfunction (acute sound) or palate disturbances. This conditions usually resolve when the treatment stops.

Hypersensitvity reactions
Very rare <0,01%):
It has been reported urticaria, high body temperature, angioedema, bronchoconstriction, or anaphylaxis shock, allergic vasculitis and fever.

Other adverse effects
Less common (1% - 0,1 %):
Peripheral Oedema (which was resolved after treatment discontinuation).

Very rare (<0,01%):
Hyponatremia, gynecomastia.

Overdose

Symptoms
There is no available information about Omeprazol's overdose effects in humans. High oral individual doses up to160 mg/day and daily oral doses up to 400 mg as well as individual intravenous doses up to 80 mg and daily intravenous doses up to 200 mg or 520 mg in 3 days, respectively, have been tolerated without adverse effects.

Pharmacological Properties

Pharmacodinamic Properties

Pharmacotherapeutic group : VII-3-b.3: Antiulcerous – proton pump inhibitor.
ATC Code: A02B C 01

The Omeprazol is a proton pump inhibitor, this mean, Omeprazol directly inhibits in a dose-dependent mode the enzyme H^+, K^+ - ATPase, which is responsible for gastric secretion from gastric parietal cells. Due to the intracellular selective mode of action, which is independent from other membrane receptors (such as histamine receptors H_2, muscarine M1 or gastric), Omeprazol has been included in a different class of acid inhibitors, which blocks the final stage of acid production.

As a consequence of its mode of action, Omeprazol leads to an inhibition of the basal acid secretion as well as the stimulated one, independently of the type of stimulation. In this way, Omeprazol increases the pH value and decreases the gastric acid secretion volume. The pro-drug Omeprazol accumulates as a weak base in the acidic environment of parietal cells

and is only effective as an H^+, K^+ - ATPase inhibitor after has been protonated and rearranged.

In an acid environment, at a pH lower than 4 the protonated Omeprazol is converted in sulfamide Omeprazol, the active form.

In comparison with Omeprazol's initial half life, the sulfamide Omeprazol lasts for a longer period in the cell (see Section " Pharmacokinetic properties"). A pH sufficiently low is only found in gastric parietal cells; this explains Omeprazol high specificity. It is the sulfamide Omeprazol that bounds to the enzyme and inhibits its activity.

If the enzymatic system is inhibited, the pH value increases and less Omeprazol accumulates or is converted within the gastric parietal cells. As a consequence, the omeprazol accumulation is regulated by a feedback mechanism.

In the long-term treatment, Omeprazol, as a result of acid inhibition, causes gastrin moderate increase. During the long-term treatments, occurs a moderate increase in the ECL cells. Carcinoid cells were found in animal trials (see 5.3.) but were not yet found in humans.

Most of the clinical experience comes from controlled clinical trials, randomized, demonstrating that Omeprazol 20 mg twice a day in association with an antibiotic during 1 week, allows to achieve an eradication rate of *H. pylori* > 80 %, in patients with gastroduodenal ulcers. As expected, were found significantly lower eradication rates in patients with isolates of *H. pylori* metronidazol-resistant. For this reason; local information about the prevalence of resistance and local treatment guidelines, should be taken in consideration, when choosing an appropriate association regimen for the eradication of *H. pylori*. Besides, in patients with persistent infections, the potencial development of secondary resistances should be considered (in patients with primary sensitive strains) to a bacterial agent, when considering a new treatment regimen.

Additionaly, the clinical evidence shows that, after the successful eradication treatment in patients with peptic ulcer, the rates of duodenal ulcers and more frequently gastric ulcers, are exceptionally low in comparison with the normal course of the disease with infection's progress. Therefore, the treatment is recommended in order to prevent peptic ulcers relapse.

Pharmacokinetic properties

Omeprazol is unstable in acid environment and is administrated as gastro-resistant granules, in hard gelatine capsules. The absorption takes place in small intestine.

The plasma concentration peaks occur between 1 and 3 hours after administration. The plasma half life is around 40 minutes and the total plasma clearance is between 0,3 and 0,6 L/min. In a small percentage of patients it has been observed a lower elimination rate of Omeprazol. In these cases, the terminal elimination half life can be approximately 3 times the normal value, and the area under the curve (AUC) can increase to 10 times more.

The Omeprazol distribution volume in the organism is relatively low (0,3 L/kg of corporal weight) and corresponds to extracellular fluid. Approximately 95 % is found protein- bound.

Omeprazol accumulates as a weak base in the acidic environment in the intracellular channel system of parietal cells. In this acid environment Omeprazol is protonated and converted in the active substance, sulfenamide Omeprazol. The active substance establishes covalent bounds to the gastric proton pump (H^+, K^+ - ATPase) in the gastric parietal cells secreting surface and inhibits its activity. The acid secretion inhibition duration is consequently bigger than the period in which the Omeprazol base is present in plasma. The acid secretion inhibition level is directly correlated with the area under the curve(AUC) concentration-time, but not with the plasma concentration at a given time.

Omeprazol is completely metabolized, mainly in the liver by CYP2C19. A small percentage of patients does not have the functional enzyme CYP2C19 and shows a low Omeprazol elimination rate. None of the metabolites has any significant anti-secretory activity. Around 20 % of the administrated dose is excreted in the faeces and the remaining 80 % are excreted in the urine as a metabolite form. The main 2 metabolites in the urine are the hydroxi-Omeprazol and the correspondent carboxylic acid. In patients with renal failure, Omeprazol kinetics is very similar to the existent in healthy individuals. Because renal elimination is the main excretion route for metabolized Omeprazol, the elimination rate is reduced in a corresponding degree to the reduction in the renal function. Accumulation can be avoided administrating Omeprazol once a day.

Omeprazol bioavailability is slightly higher in the elderly, and the elimination rate is slightly decreased. But the individual values are approximately the same comparing to healthy young individuals, and there is no indication that tolerance in elderly individuals with normal Omeprazol doses is decreased.

After the intravenous administration of 40 mg of Omeprazol during 5 days, the absolute bioavailability measured increased around 50 %; this can be explained by the decrease in hepatic clearance due to enzyme CYP2C19 saturation.

In patients with chronic hepatic disease, Omeprazol clearance is low and the plasma half life can increase until approximately 3 hours. The bioavailability can be higher then 90 %. The administrated Omeprazol in a 20 mg once a day regimen during 4 weeks was well tolerated and there was no accumulation of Omeprazol or its metabolites.

Bioavailability

Bioavailability of an Omeprazol single oral dose is approximately 35 %. With repeated administration, bioavailability increases approximately to 60 %. In patients with limited hepatic function, bioavailability can increase to 90 % due the reduction of first pass effect.

Preclinical safety data

There is no research data about chronic toxicity that suggest adverse effects occurrence unknown until now, in humans.

In long-term studies corresponding to a rat's life, in rats treated with Omeprazol or exposed to partial fundectomy, was found hyperplasia of the gastric ECL and carcinoid cells. This alteration is a result of a maintained hypergastrinemia secondary to acid inhibition.

In mutagenicity studies (*in vitro* or *in vivo*) did not occur any clinical relevant results

Pharmaceutical particulars

List of excipients

Gasec® 10, Gasec® 20, Gasec® 40:

Granule with gastro-resistant cover: Neutral granules, hydroxipropyl-metilcelulose, dibasic sodium phosphate, Syloid 244, titanium dioxide (E 171), Eudragit L30 D, Citroflex 2, talc.

Capsule Composition: Gelatin, titanium dioxide (E 171), iron oxide (E 172), indigotine (E 132).

Incompatibilities

None described.

Precautions for storage

Keep in a fresh and dry place below 25° C.

Do not use this medication after the expiry date stated "EXP" on the packaging.

Nature and contents of container

White bottle of high density polyethylene (HDPE) with cap and exsiccant.

Instructions for use/Handling

Keep out of the reach and sight of children.

Presentation

Gasec-10: Packings of 14 and 28 Gastrocaps.
Gasec-20: Packings of 7, 14, 28 and 56 Gastrocaps.
Gasec-40: Packings of 14 and 28 Gastrocaps.

Date of revision of the text

March 2002

THIS IS A MEDICAMENT

Medicament is a product which affects your health and its consumption contrary is dangerous for you.

Follow strictly the doctor's prescription, the method of use and the instructions of the Pharmacist who sold the medication.

- The Doctor and Pharmacist are experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of reach

Council of Arab Health Ministers,
Union of Arab Pharmacist

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