

Vaxcel®

ESOMEPRAZOLE 40mg

POWDER FOR INJECTION

COMPOSITION:

Each vial contains:
Esomeprazole Sodium
equivalent to Esomeprazole 40mg

PRESENTATION:

A white or almost white powder, which gives clear and colourless to very slightly yellow solution after reconstitution.

INDICATIONS:

Vaxcel Esomeprazole 40mg for injection and infusion is indicated for:

- Gastric antisecretory treatment when the oral route is not possible, such as:
 - gastroesophageal reflux disease (GERD) in patients with esophagitis and/or severe symptoms of reflux.
 - healing of gastric ulcers associated with NSAID therapy.
 - prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk.
- Prevention of rebleeding following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.

PHARMACOLOGY:

Mechanism of Action:

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H⁺K⁺-ATPase – the acid pump and inhibits both basal and stimulated acid secretion. Esomeprazole is the S-isomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. Pharmacotherapeutic group: Drugs for acid-related disorders, proton pump inhibitor. ATC Code: A02B C05.

Effect on Gastric Acid Secretion:

After 5 days of oral dosing with 20mg and 40mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours respectively, over 24 hours in symptomatic gastroesophageal reflux disease (GORD) patients. The effect is similar irrespective of whether esomeprazole is administered orally or intravenously. Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown after oral administration of esomeprazole. During intravenous administration of 80mg esomeprazole as a bolus infusion over 30 minutes followed by a continuous intravenous infusion of 8 mg/h for 23.5 hours, intragastric pH above 4, and pH above 6 was maintained for a mean time of 21 hours, and 11-13 hours, respectively, over 24 hours in healthy subjects.

Therapeutic Effects of Acid Inhibition:

Healing of reflux esophagitis with esomeprazole 40mg occurs in approximately 78% of patients after 4 weeks, and in 93% after 8 weeks of oral treatment.

Other Effects Related To Acid Inhibition:

During treatment with antisecretory drugs serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. Available published evidence

suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range. An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in both children and adults during long-term treatment with esomeprazole. The findings are considered to be of no clinical significance. During long-term oral treatment with antisecretory medicinal products, gastric glandular cysts have been reported to occur at a somewhat increased frequency. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible. Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Pharmacokinetics:

Distribution:

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22L/kg body weight. Esomeprazole is 97% plasma protein bound.

Metabolism and Excretion:

Biotransformation:

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulfone, the main metabolite in plasma.

Elimination:

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers. Total plasma clearance is about 17L/h after a single dose and about 9L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration. The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of esomeprazole is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent medicinal product is found in urine.

Linearity / Non-Linearity:

Total exposure (AUC) increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by inhibition of the CYP2C19 enzyme by esomeprazole and / or its sulfone metabolite. Following repeated doses of 40mg administered as intravenous injections, the mean peak plasma concentration is approx. 13.6 micromol/L. The mean peak plasma concentration after corresponding oral doses is approx. 4.6 micromol/L. A smaller increase (of approx. 30%) can be seen in total exposure after intravenous administration compared to oral administration. There is a dose-linear increase in total exposure following intravenous administration of esomeprazole as a 30-minute infusion (40mg, 80mg or 120mg) followed by a continuous infusion (4mg/h or 8mg/h) over 23.5 hours.

Special Patient Populations:

Poor metabolisers:

Approximately 2.9 ± 1.5% of the population lacks a functional CYP2C19 enzyme and is called poor metabolisers. In these individuals, the metabolism of esomeprazole is probably mainly catalysed by CYP3A4. After repeated once-daily administration of 40mg oral esomeprazole, the mean total exposure was approximately 100% higher in poor metabolisers than in subjects with a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60%. Similar differences have been seen for intravenous administration of esomeprazole. These findings have no implications for the dosing of esomeprazole.

Gender:

Following a single oral dose of 40mg esomeprazole the mean total exposure is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. Similar differences have been observed for intravenous administration of esomeprazole. These findings have no implications for the dosing of esomeprazole.

Hepatic Impairment:

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction

may be impaired. The metabolic rate is decreased in patients with severe liver dysfunction resulting in a doubling of the total exposure of esomeprazole. Therefore, a maximum dose of 20mg should not be exceeded in GERD patients with severe dysfunction. For patients with bleeding ulcers and severe liver impairment, following an initial bolus dose of 80mg, a maximum continuous intravenous infusion dose of 4 mg/h for 71.5 hours may be sufficient. Esomeprazole or its major metabolites do not show any tendency to accumulate with once-daily dosing.

Renal Impairment:

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Elderly People:

The metabolism of esomeprazole is not significantly changed in elderly subjects (71- 80 years of age).

DIRECTION FOR USE:

Adults:

Gastric Antisecretory Treatment When The Oral Route Is Not Possible:

Patients who cannot take oral medication may be treated parenterally with 20-40mg once daily. Patients with reflux esophagitis should be treated with 40mg once daily. Patients treated symptomatically for reflux disease should be treated with 20mg once daily. For healing of gastric ulcers associated with NSAID therapy the usual dose is 20mg once daily. For prevention of gastric and duodenal ulcers associated with NSAID therapy, patients at risk should be treated with 20mg once daily. Usually the intravenous treatment duration is short and transfer to oral treatment should be made as soon as possible.

Prevention of Rebleeding of Gastric and Duodenal Ulcers:

Following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers, 80mg should be administered as a bolus infusion over 30 minutes, followed by a continuous intravenous infusion of 8mg/h given over 3 days (72 hours). The parenteral treatment period should be followed by oral acid suppression therapy.

Method of Administration:

For preparation of reconstituted solution, see Instruction for Use and Handling.

Injection:

40mg dose: 5ml of the reconstituted solution (8mg/ml) should be given as an intravenous injection over a period of at least 3 minutes.

20mg dose: 2.5ml or half of the reconstituted solution (8mg/ml) should be given as an intravenous injection over a period of at least 3 minutes.

Infusion:

40mg dose: The reconstituted solution should be given as an intravenous infusion over a period of 10 to 30 minutes.

20mg dose: Half of the reconstituted solution should be given as an intravenous infusion over a period of 10 to 30 minutes.

80mg bolus dose: The reconstituted solution should be given as a continuous intravenous infusion over 30 minutes.

8mg/h dose: The reconstituted solution should be given as a continuous intravenous infusion over a period of 71.5 hours (calculated rate of infusion of 8mg/h).

Special Populations:

Children and adolescents

Vaxcel Esomeprazole 40mg Powder for Injection should not be used in children since no data is available.

Patients with Impaired Renal Function:

Dose adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency, such patients should be treated with caution (see Pharmacokinetics).

Patients with Impaired Hepatic Function:

GERD: Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, a maximum daily dose of 20mg Vaxcel Esomeprazole 40mg Powder for Injection i.v. should not be exceeded (see section Pharmacokinetics).

Bleeding ulcers: Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, following an initial bolus dose of 80mg Vaxcel Esomeprazole 40mg Powder for Injection for infusion, a

continuous intravenous infusion dose of 4mg/h for 71.5 hours may be sufficient (see Pharmacokinetics).

Older People: Dose adjustment is not required in the elderly.

Instruction for Use and Handling:

The reconstituted solution should be inspected visually for particulate matter and discoloration prior to administration. Only clear solution should be used. The degradation of reconstituted solution is highly pH dependent and the product must therefore only be reconstituted in the specified volume of 0.9% sodium chloride for intravenous use. The reconstituted solution should not be mixed or co-administered in the same infusion set with any other drug. From a microbiological point of view, the product is recommended to be used immediately. For single use only.

If the entire reconstituted content of the vial is not required, any unused solution should be discarded in accordance with local requirements.

Injection:

Injection 40mg: A solution for injection (8mg/ml) is prepared by adding 5 ml of 0.9% sodium chloride for intravenous use to the esomeprazole 40 mg vial. The reconstituted solution for injection is clear and colourless to very slightly yellow. The reconstituted solution should be given as an intravenous injection over a period of at least 3 minutes. Half of the volume should be given if 20mg should be administered. Any unused solution after 12 hours should be discarded.

Infusion:

Infusion 40mg: A solution for infusion is prepared by dissolving the content of one vial with esomeprazole 40mg in up to 100ml of 0.9% sodium chloride for intravenous use. Half of the volume should be given if 20mg should be administered. Any unused solution after 12 hours should be discarded.

Infusion 80mg: A solution for infusion is prepared by dissolving the contents of two vials of esomeprazole 40mg in up to 100ml of 0.9% sodium chloride for intravenous use.

The reconstituted solution for infusion is clear and colourless to very slightly yellow. The reconstituted solution should be given as an intravenous infusion over a period of 10 to 30 minutes.

Route of Administration: for intravenous injection & infusion only.

CONTRAINDICATIONS:

Hypersensitivity to the active substance esomeprazole or to other substituted benzimidazoles or to any of the excipients of this medicinal product. Esomeprazole should not be used concomitantly with nelfinavir (see Interaction).

PRECAUTIONS:

In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with Vaxcel Esomeprazole 40mg Powder for Injection may alleviate symptoms and delay diagnosis.

Gastrointestinal Infections:

Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

Absorption of Vitamin B12:

Esomeprazole, as all acid-blocking medicines, may reduce the absorption of Vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced Vitamin B12 absorption on long-term therapy.

Hypomagnesaemia:

Severe hypomagnesaemia has been reported in patients treated with PPI like Esomeprazole Sodium for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPI with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

MAL18071005AZ

Fracture:

Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognized risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10-40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of Vitamin D and Calcium.

Subacute Cutaneous Lupus Erythematosus (SCLE):

Proton pump inhibitors are associated with very infrequent cases of subacute cutaneous lupus erythematosus (SCLE). If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping Vaxcel Esomeprazole 40mg Powder for Injection. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Serious Cutaneous Adverse Reactions (SCARs)

Serious cutaneous adverse reactions (SCARs) such as erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening, have been reported very rarely in association with esomeprazole treatment. Patients should be advised of the signs and symptoms of the severe skin reaction EM/SJS/TEN/DRESS and should seek medical advice from their physician immediately when observing any indicative signs or symptoms. Esomeprazole should be discontinued immediately upon signs and symptoms of severe skin reactions and additional medical care/close monitoring should be provided as needed. Re-challenge should not be undertaken in patients with EM/SJS/TEN/DRESS.

Combination with Other Medicines:

Co-administration of esomeprazole with atazanavir is not recommended. If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of atazanavir to 400mg with 100mg of ritonavir; esomeprazole 20mg should not be exceeded.

Esomeprazole is a CYP2C19 inhibitor. When starting or ending treatment with esomeprazole, the potential for interactions with drugs metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and esomeprazole (see "Interactions"). The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of esomeprazole and clopidogrel should be discouraged.

Interference with Laboratory Tests:

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, esomeprazole treatment should be stopped for at least 5 days before CgA measurements. If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

Regular Surveillance:

Patients on proton pump inhibitor treatment (particularly those treated for long term) should be kept under regular surveillance.

SIDE EFFECTS:

The following adverse medicinal product reactions have been identified or suspected for esomeprazole administered orally or intravenously.

System Organ Class	Frequency	Undesirable Effect
Blood and lymphatic system disorder	Rare	Leukopenia, thrombocytopenia
	Very rare	Agranulocytosis, pancytopenia
Immune system disorders	Rare	Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock
Metabolism and nutrition disorders	Uncommon	Peripheral edema
	Rare	Hyponatremia
	Not known	Hypomagnesaemia, severe hypomagnesaemia may result in hypocalcaemia, hypomagnesaemia may also result in hypokalaemia,
	Not known	Vitamin B12 deficiency

System Organ Class	Frequency	Undesirable Effect
Psychiatric disorders	Uncommon	Insomnia
	Rare	Agitation, confusion, depression
	Very rare	Aggression, hallucinations
Nervous system disorders	Common	Headache
	Uncommon	Dizziness, paraesthesia, somnolence
	Rare	Taste disturbance
Eye disorders	Uncommon	Blurred vision
Ear and labyrinth disorders	Uncommon	Vertigo
Respiratory, thoracic and mediastinal disorders	Rare	Bronchospasm
Gastrointestinal disorders	Common	Abdominal pain, constipation, diarrhea, flatulence, nausea/vomiting, Fundic gland polyps (benign)
	Uncommon	Dry mouth
	Rare	Stomatitis, gastrointestinal candidiasis
	Not known	Microscopic colitis
Hepatobiliary disorders	Uncommon	Increased liver enzymes
	Rare	Hepatitis with or without jaundice
	Very rare	Hepatic failure, encephalopathy in patients with pre-existing liver disease
Skin and subcutaneous tissue disorders	Common	Administration site reactions*
	Uncommon	Dermatitis, pruritus, rash, urticaria
	Rare	Alopecia, photosensitivity
	Very rare	Erythema multiforme, Stevens-Johnson syndrome, Toxic Epidermal Necrolysis (TEN), Acute Generalised Exanthematous Pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS)
	Not known	Subacute cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders	Uncommon	Fracture of the hip, wrist or spine
	Rare	Arthralgia, myalgia
	Very rare	Muscular weakness
Renal and urinary disorders	Very rare	Interstitial nephritis
	Very rare	Gynaecomastia
Reproductive system and breast disorders	Very rare	
General disorders and administration site conditions	Rare	Malaise, increased sweating
Infections & infestations	Not known	Clostridium difficile associated diarrhea

*Administration site reactions have mainly been observed in a study with high-dose exposure over 3 days (72 hours). Irreversible visual impairment has been reported in isolated cases of critically ill patients who have received omeprazole (the racemate) intravenous injection, especially at high doses, but no causal relationship has been established.

DRUG INTERACTION:

Effects of esomeprazole on the pharmacokinetics of other medicinal products.

Medicinal products with pH dependent absorption :

Gastric acid suppression during treatment with esomeprazole and other PPIs might decrease or increase the absorption of medicinal products drugs with a gastric pH dependent absorption. As with other medicinal products that decrease the intragastric acidity, the absorption of medicinal products, such as ketoconazole, itraconazole and erlotinib and the absorption of digoxin can increase during treatment with esomeprazole. Digoxin toxicity has been rarely reported. However, caution should be exercised when esomeprazole is given at high doses in elderly patients. Therapeutic drug monitoring of digoxin should then be reinforced.

Protease inhibitors:

Omeprazole has been reported to interact with some protease inhibitors. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the protease inhibitors. Other possible interaction mechanisms are via inhibition of CYP 2C19. For atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and atazanavir is not recommended and concomitant administration with esomeprazole and nelfinavir is contraindicated.

Medicinal products metabolised by CYP2C19 :

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with medicinal products metabolised by CYP2C19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these medicinal products may be increased and a dose reduction could be needed.

No *in vivo* interaction studies have been performed with the high dose intravenous regimen (80 mg+8 mg/h). The effect of esomeprazole on medicinal products metabolised by CYP2C19 may be more pronounced during this regimen, and patients should be monitored closely for adverse effects, during the 3 days intravenous treatment period.

Diazepam :

Concomitant oral administration of 30mg esomeprazole resulted in a 45% decrease in clearance of the CYP2C19 substrate diazepam.

Phenytoin :

Concomitant oral administration of 40mg esomeprazole and phenytoin resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Voriconazole :

Omeprazole (40mg once daily) increased voriconazole (a CYP2C19 substrate) Cmax and AUCt by 15% and 41%, respectively.

Clostellazol :

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased Cmax and AUC for clostellazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.

Cisapride :

Concomitant oral administration of 40mg esomeprazole and cisapride resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life (t1/2) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole.

Warfarin :

Monitoring is recommended when initiating and ending concomitant esomeprazole treatment during treatment with warfarin or other coumarine derivatives.

Clopidogrel :

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were the same in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

Amoxicillin or quinidine :

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Effects of other medicinal products on the pharmacokinetics of esomeprazole

Medicinal products which inhibit CYP2C19 and/or CYP3A4 :

Esomeprazole is metabolised by CYP2C19 and CYP3A4. Concomitant oral administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500mg b.i.d.), resulted in a doubling of the exposure (AUC) to esomeprazole. Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4 may result in more than doubling of the esomeprazole exposure. The CYP2C19

and CYP3A4 inhibitor voriconazole increased omeprazole AUCt by 280%. A dose adjustment of esomeprazole is not regularly required in either of these situations. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Medicinal products which induce CYP2C19 and/or CYP3A4 :

Medicinal products known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Unknown mechanism

Tacrolimus :

Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus.

Methotrexate :

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

Incompatibilities :

This medicinal product should not be used with other medicinal products except those mentioned in *Instruction for Use and Handling*.

Pregnancy and Lactation :

Pregnancy

For esomeprazole limited data on exposed pregnancies are available. Animal studies with esomeprazole do not indicate direct or indirect harmful effects with respect to embryonal / foetal development. Animal studies with the racemic mixture do not indicate direct or indirect harmful effects with respect to pregnancy, parturition or postnatal development. Caution should be exercised when prescribing Vaxcel Esomeprazole 40mg Powder for Injection to pregnant women.

Breast-Feeding

It is not known whether esomeprazole is excreted in human breast milk. No studies in lactating women have been performed. Therefore Vaxcel Esomeprazole 40mg Powder for Injection should not be used during breast feeding.

Effects on Ability To Drive and Use Machines :

Esomeprazole is not likely to affect the ability to drive or use machines.

OVERDOSAGE AND TREATMENT :

There is very limited experience to date with deliberate overdose. The symptoms described in connection with an oral dose of 280mg were gastrointestinal symptoms and weakness. Single oral doses of 80mg esomeprazole and intravenous doses of 308mg esomeprazole over 24 hours were uneventful. No specific antidote is known. Esomeprazole is extensively plasma protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilized.

STORAGE:

The powder vial should be stored below 30°C. Reconstituted solution can be stored for 12 hours below 30°C. From a microbiological point of view, the product should be used immediately.

KEEP OUT OF REACH OF CHILDREN

JAUHI DARI KANAK-KANAK

PACK QUANTITIES:

One vial & 10 vials of sterile powder for injection per box. Not all pack sizes may be marketed.

Further information can be obtained from pharmacist, physician or the manufacturer.

Product Registration Holder & Manufactured By :

 **Kotra Pharma (M) Sdn. Bhd.**
No. 1, 2 & 3, Jalan TTC 12, (90082-V)
Cheng Industrial Estate,
75250 Melaka, Malaysia.