HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NEXIUM I.V. safely and effectively. See full prescribing information for NEXIUM I.V.

NEXIUM® I.V. (esomeprazole sodium) for injection, for intravenous use

Initial U.S. Approval: 2005

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**INDICATIONS AND USAGE**

NEXIUM I.V. is a proton pump inhibitor indicated for the treatment of:

- Gastroesophageal Reflux Disease (GERD) with erosive esophagitis (EE) in adults and pediatric patients greater than one month of age, when oral therapy is not possible or appropriate. (1.1)
- Risk Reduction of Rebleeding of Gastric or Duodenal Ulcers following therapeutic endoscopy in adults. (1.2)

**DOSE AND ADMINISTRATION**

GERD — with Erosive Esophagitis. (2.1):
- Adults: Dose is either 20 mg or 40 mg NEXIUM given once daily by intravenous injection (no less than 3 minutes) or intravenous infusion (10 minutes to 30 minutes).
- Pediatric: Give the following doses once daily as an intravenous infusion over 10 minutes to 30 minutes. (2.1):
  - 1 year to less than 12 years:体 weight less than 55 kg: 10 mg
  - Body weight 55 kg or greater: 20 mg
  - Body weight less than 1 year of age: 0.5 mg/kg
- For patients with severe liver impairment (Child-Pugh Class C), a maximum dose of 20 mg once daily of NEXIUM should not be exceeded. (2.1, 8.6, 12.3)

Risk Reduction of Rebleeding of Gastric and Duodenal Ulcers in the first 72 hours following therapeutic endoscopy in Adults. (2.2):
- 80 mg intravenous infusion given over 30 minutes, followed by a continuous infusion of 8 mg/h over 3 days (72 hours).
- Dose adjustments are needed in patients with liver impairment. (2.2, 8.6, 12.3)
- For patients with bleeding gastric or duodenal ulcers and mild to moderate liver impairment (Child-Pugh Classes A and B), a maximum continuous infusion of 6 mg/h should not be exceeded.
- For patients with severe liver impairment (Child-Pugh Class C), a maximum continuous infusion of 4 mg/h should not be exceeded.

**DOSE FORMS AND STRENGTHS**

NEXIUM I.V. for injection is supplied as a freeze-dried powder containing 20 mg or 40 mg of esomeprazole per single-use vial. (3)

**CONTRAINDICATIONS**

Patients with known hypersensitivity to any component of the formulation or to substituted benzimidazoles (angioedema and anaphylaxis have occurred). (4)

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**WARNINGS AND PRECAUTIONS**

- Gastric Malignancy: In adults, symptomatic response to therapy with NEXIUM I.V. does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing. (5.1)
- Acute Interstitial Nephritis: Observed in patients taking PPIs. (5.2)
- Clostridium difficile-Associated Diarrhea: PPI therapy may be associated with increased risk. (5.3)
- Bone Fracture: Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. (5.4)
- Cutaneous and Systemic Lupus Erythematosus: Mostly cutaneous; new onset or exacerbation of existing disease; discontinue NEXIUM I.V. and refer to specialist for evaluation. (5.5)
- Interaction with Clopidogrel: Avoid concomitant use of NEXIUM I.V. (5.6)
- Hypomagnesemia: Reported rarely with prolonged treatment with PPIs. (5.7)
- Interaction with St. John’s Wort or Rifampin: Avoid concomitant use of NEXIUM I.V. (5.8, 7.2)
- Interactions with Diagnostic Investigations for Neuroendocrine Tumors: Increased chromogranin A (CgA) levels may interfere with diagnostic investigations for neuroendocrine tumors; temporarily stop NEXIUM I.V. at least 14 days before assessing CgA levels. (5.9, 12.2)
- Interaction with Methotrexate: Concomitant use with PPIs may elevate and/or prolong serum concentrations of methotrexate and/or its metabolite, possibly leading to toxicity. With high dose methotrexate administration, consider a temporary withdrawal of NEXIUM I.V. (5.10, 7.3)
- Fundic Gland Polyps: Risk increases with long-term use, especially beyond one year. Use the shortest duration of therapy. (5.11)

**ADVERSE REACTIONS**

Most common adverse reactions (≥1%) are headache, flatulence, nausea, abdominal pain, injection site reaction, diarrhea, dry mouth, dizziness/vertigo, constipation and pruritus. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**DRUG INTERACTIONS**

- NEXIUM I.V. may interfere with drugs for which gastric pH affects bioavailability (e.g., ketoconazole, iron salts, erlotinib, digoxin and mycophenolate mofetil). Patients treated with NEXIUM I.V. and digoxin may need to be monitored for digoxin toxicity. (7)
- Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time. (7)
- NEXIUM I.V. may reduce the plasma levels of atazanavir, neflinavir, and saquinavir. (7)
- Concomitant treatment with a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. (7)
- May increase systemic exposure of cilostazol and an active metabolite. Consider dose reduction. (7)
- Clopidogrel: NEXIUM I.V. decreases exposure to the active metabolite of clopidogrel. (7)
- Tacrolimus: NEXIUM I.V. may increase serum levels of tacrolimus. (7.2)
- Methotrexate: NEXIUM I.V. may increase serum levels of methotrexate. (7.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 08/2018

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NEXIUM® I.V. (esomeprazole sodium) for Injection

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Gastroesophageal Reflux Disease (GERD) with Erosive Esophagitis
NEXIUM I.V. for Injection is indicated for the short-term treatment of GERD with erosive esophagitis in adults and pediatric patients 1 month to 17 years, inclusively as an alternative to oral therapy when oral NEXIUM is not possible or appropriate.

1.2 Risk Reduction of Rebleeding of Gastric or Duodenal Ulcers following Therapeutic Endoscopy in Adults
NEXIUM I.V. for Injection is indicated for risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers in adults.

2 DOSAGE AND ADMINISTRATION

General Information
NEXIUM I.V. for Injection should not be administered concomitantly with any other medications through the same intravenous site and/or tubing. The intravenous line should always be flushed with either 0.9% Sodium Chloride Injection, USP, Lactated Ringer’s Injection, USP or 5% Dextrose Injection, USP both prior to and after administration of NEXIUM I.V. for Injection.
The admixture should be stored at room temperature up to 30°C (86°F) and should be administered within the designated time period as listed in Table 1 below. No refrigeration is required.

Table 1: Storage Time for Final (diluted) Product

<table>
<thead>
<tr>
<th>Diluent</th>
<th>Administer within:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9% Sodium Chloride Injection, USP</td>
<td>12 hours</td>
</tr>
<tr>
<td>Lactated Ringer’s Injection, USP</td>
<td>12 hours</td>
</tr>
<tr>
<td>5% Dextrose Injection, USP</td>
<td>6 hours</td>
</tr>
</tbody>
</table>

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

As soon as oral therapy is possible or appropriate, intravenous therapy with NEXIUM I.V. for Injection should be discontinued and the therapy should be continued orally.

2.1 GERD with Erosive Esophagitis

Adult Patients
The recommended adult dose is either 20 mg or 40 mg NEXIUM given once daily by intravenous injection (no less than 3 minutes) or intravenous infusion (10 minutes to 30 minutes). Safety and efficacy of NEXIUM I.V. for Injection as a treatment of GERD patients with erosive esophagitis for more than 10 days have not been demonstrated.

Dosage adjustment is not required in patients with mild to moderate liver impairment (Child-Pugh Classes A and B). For patients with severe liver impairment (Child-Pugh Class C), a maximum dose of 20 mg once daily of NEXIUM should not be exceeded [see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)].

Pediatric Patients
The recommended doses for children ages 1 month to 17 years, inclusive, are provided below. Dose should be infused over 10 minutes to 30 minutes.

1 year to 17 years:
- Body weight less than 55 kg: 10 mg
- Body weight 55 kg or greater: 20 mg
1 month to less than 1 year of age: 0.5 mg/kg

2.2 Risk Reduction of Rebleeding of Gastric or Duodenal Ulcers following Therapeutic Endoscopy in Adults

Adult dose is 80 mg administered as an intravenous infusion over 30 minutes followed by a continuous infusion of 8 mg/h for a total duration of treatment 72 hours (i.e., includes initial 30-minute dose plus 71.5 hours of continuous infusion). Intravenous therapy is aimed solely at the acute initial management of bleeding gastric or duodenal ulcers and does not constitute full treatment. Intravenous therapy should be followed by oral acid-suppressive therapy.

For patients with liver impairment, no dosage adjustment of the initial esomeprazole 80 mg infusion is necessary. For patients with mild to moderate liver impairment (Child-Pugh Classes A and B), a maximum continuous infusion of esomeprazole 6 mg/h should not be exceeded. For patients with severe liver impairment (Child-Pugh Class C), a maximum continuous infusion of 4 mg/h should not be exceeded [see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)].

2.3 Preparation and Administration Instructions

General Information
The reconstituted solution of NEXIUM I.V. should be stored at room temperature up to 30°C (86°F) and administered within 12 hours after reconstitution. (Administer within 6 hours if 5% Dextrose Injection is used after reconstitution). No refrigeration is required [see Dosage and Administration (2), Table 1].

Gastroesophageal Reflux Disease (GERD) with Erosive Esophagitis
Preparation Instructions for Adult Patients
Intravenous Injection (20 mg or 40 mg vial) over no less than 3 minutes
The freeze-dried powder should be reconstituted with 5 mL of 0.9% Sodium Chloride Injection, USP.
Withdraw 5 mL of the reconstituted solution and administer as an intravenous injection over no less than 3 minutes.

Preparation Instructions for Pediatric Patients
Intravenous Infusion (20 mg or 40 mg) over 10 minutes to 30 minutes
A solution for intravenous infusion is prepared by first reconstituting the contents of one vial with 5 mL of 0.9% Sodium Chloride Injection, USP, Lactated Ringer’s Injection, USP or 5% Dextrose Injection, USP and further diluting the resulting solution to a final volume of 50 mL. The resultant concentration after diluting to a final volume of 50 mL is 0.8 mg/mL (for 40 mg vial) and 0.4 mg/mL (for 20 mg vial). The solution (admixture) should be administered as an intravenous infusion over a period of 10 minutes to 30 minutes.

*For patients 1 month to less than 1 year of age, first calculate the dose (0.5 mg/kg) to determine the vial size needed.

Risk Reduction of Rebleeding of Gastric or Duodenal Ulcers in Adults
Preparation Instructions for Loading dose (80 mg) to be given over 30 minutes
The loading dose of 80 mg is prepared by reconstituting two 40 mg vials. Reconstitute each 40 mg vial with 5 mL of 0.9% Sodium Chloride Injection, USP. The contents of the two vials should be further diluted in 100 mL 0.9% Sodium Chloride Injection, USP for intravenous use. Administer over 30 minutes.

Preparation Instructions for Continuous Infusion to be given at 8 mg/hour for 71.5 hours
The continuous infusion is prepared by using two 40 mg vials. Reconstitute each 40 mg vial with 5 mL each of 0.9% Sodium Chloride Injection, USP. The contents of the two vials should be further diluted in 100 mL 0.9% Sodium Chloride Injection, USP for intravenous use. Administer at a rate of 8 mg/hour for 71.5 hours.

3 DOSAGE FORMS AND STRENGTHS

NEXIUM I.V. for Injection is supplied as a freeze-dried white to off-white powder containing 20 mg or 40 mg of esomeprazole per single-use vial.

4 CONTRAINDICATIONS

NEXIUM I.V. is contraindicated in patients with known hypersensitivity to substituted benzimidazoles or to any component of the formulation. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasms, acute interstitial nephritis, and urticaria [see Adverse Reactions (6)].

5 WARNINGS AND PRECAUTIONS

5.1 Presence of Gastric Malignancy
In adults, symptomatic response to therapy with NEXIUM I.V. does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing in adults patients who have suboptimal response or an early symptomatic relapse after completing treatment with a PPI. In older patients also consider an endoscopy.

5.2 Acute Interstitial Nephritis
Acute interstitial nephritis has been observed in patients taking PPIs including NEXIUM I.V. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiosyncratic hypersensitivity reaction. Discontinue NEXIUM I.V. if acute interstitial nephritis develops [see Contraindications (4)].

5.3 Closstridium difficile-Associated Diarrhea
Published observational studies suggest that PPI therapy like NEXIUM may be associated with an increased risk of Closstridium difficile-associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve [see Adverse Reactions (6.2)].

Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

5.4 Bone Fracture
Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines [see Dosage and Administration (2) and Adverse Reactions (6.2)].

5.5 Cutaneous and Systemic Lupus Erythematosus
Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs, including esomeprazole. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematosus cases were CLE.

The most common form of CLE reported in patients treated with PPIs was subacute CLE and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly. Generally, histological findings were observed without organ involvement.

Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug induced SLE. Onset of SLE typically occurred within days to years after initiating treatment primarily in patients ranging from young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopenia were also reported.

Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving NEXIUM I.V., discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in 4 to 12 weeks. Serological testing (e.g., ANA) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.
Intravenous treatment with esomeprazole 20 and 40 mg administered as an injection or as an infusion was found to be a similar safety profile to that of oral administration of esomeprazole.

**Pediatric**

A randomized, open-label, multi-national study to evaluate the pharmacokinetics of repeated intravenous doses of once daily esomeprazole in pediatric patients 1 month to 17 years old, inclusive was performed. The safety results are consistent with the known safety profile of esomeprazole and no unexpected safety signals were identified [see Clinical Pharmacology (12.3)].

**Risk Reduction of Rebleeding of Gastric or Duodenal Ulcers in Adults**

The data described below reflect exposure to NEXIUM I.V. for injection in 375 patients. NEXIUM I.V. for injection was studied in a placebo-controlled trial. Patients were randomized to receive NEXIUM I.V. for injection (n=375) or placebo (n=389). The population was 18 to 98 years old; 68% Male, 87% Caucasian, 1% Black, 7% Asian, 4% Other, who presented with endoscopically confirmed gastric or duodenal ulcer bleeding. Following endoscopic hemostasis, patients received either 80 mg esomeprazole as an intravenous infusion over 30 minutes followed by a continuous infusion of 8 mg per hour for a total treatment duration of 72 hours. After the initial 72-hour period, all patients received oral proton pump inhibitor (PPI) for 27 days.

**Table 3: Incidence (%) of Adverse Reactions that Occurred in Greater than 1% of Patients within 72 Hours After Start of Treatment**

| Adverse Reaction       | Esomeprazole (n=375) | Placebo (n=389) |
|-------------------------|----------------------|----------------|}

**5.6 Interaction with Captopril**

Avoid concomitant use of NEXIUM I.V. with cilnidipine. Captopril is a prodrug. Inhibition of platelet aggregation by cilnidipine is entirely due to its active metabolite. The metabolism of cilnidipine to its active metabolite can be impaired by use with concomitant medications, such as esomeprazole, which inhibit CYP2C19 activity. Concomitant use of cilnidipine with 40 mg esomeprazole reduces the pharmacological activity of cilnidipine. When using NEXIUM I.V. consider alternative anti-platelet therapy [see Drug Interactions (7). Clinical Pharmacology (12.3)].

**5.7 Hypomagnesemia**

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), healthcare professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically [see Adverse Reactions (6.2)].

**5.8 Interaction with St John’s Wort or Rifampin**

Drugs which induce CYP2C19 or CYP3A4 (such as St John’s Wort or rifampin) can substantially decrease esomeprazole concentrations [see Drug Interactions (7)]. Avoid concomitant use of NEXIUM with St John’s Wort or rifampin.

**5.9 Interactions with Diagnostic Investigations for Neuroendocrine Tumors**

Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. Healthcare providers should temporarily stop esomeprazole treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g., for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary [see Clinical Pharmacology (12.2)].

**5.10 Interaction with Methotrexate**

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolites, possibly leading to methotrexate toxicities. In high-dose methotrexate administration, a temporary withdrawal of the PPI may be considered in some patients [see Drug Interactions (7.3)].

**5.11 Fundic Gland Polyps**

PPI use is associated with an increased risk of fundic gland polyps that increases with long-term use, especially beyond one year. Most PPI users who developed fundic gland polyps were asymptomatic and fundic gland polyps were identified incidentally on endoscopy. Use the shortest duration of PPI therapy appropriate to the condition being treated.

**6 ADVERSE REACTIONS**

The following serious adverse reactions are described below and elsewhere in labeling:

- Acute Intestinal Nephritis [see Warnings and Precautions (5.2)]
- Clostridium difficile-Associated Diarrhea [see Warnings and Precautions (5.3)]
- Bone Fracture [see Warnings and Precautions (5.4)]
- Cutaneous and Systemic Lupus Erythematosus [see Warnings and Precautions (5.5)]
- Hypomagnesemia [see Warnings and Precautions (5.7)]
- Fundic Gland Polyps [see Warnings and Precautions (5.11)]

**6.1 Clinical Trials Experience with Intravenous NEXIUM**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

**Adults**

The safety of intravenous esomeprazole is based on results from clinical trials conducted in four different populations including patients having symptomatic GERD with or without a history of erosive esophagitis (n=199), patients with erosive esophagitis (n=160), healthy subjects (n=204) and patients with bleeding gastric or duodenal ulcers (n=375).

**Symptomatic GERD and Erosive Esophagitis Trials**

The data described below reflect exposure to NEXIUM I.V. for Injection in 359 patients. NEXIUM I.V. for injection was studied only in actively-controlled trials. The population was 18 to 77 years old; 45% Male, 45% Female, 52% Caucasian, 17% Black, 3% Asian, 28% Other, and had either erosive reflux esophagitis (44%) or GERD (56%). Most patients received doses of 18 to 77 years of age; 45% Male, 52% Caucasian, 17% Black, 3% Asian, 28% Other, and had a history of erosive esophagitis (n=199), patients with erosive esophagitis (n=160), healthy patients (n=389).

**Table 2: Adverse Reactions Occurring at an Incidence ≥ 1% in the NEXIUM I.V. Group**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>% of patients (n=359)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>10.3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6.4</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5.8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.9</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>3.9</td>
</tr>
<tr>
<td>Dizziness/vertigo</td>
<td>2.8</td>
</tr>
<tr>
<td>Constipation</td>
<td>2.5</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>1.7</td>
</tr>
<tr>
<td>Pruritis</td>
<td>1.1</td>
</tr>
</tbody>
</table>

**Postmarketing Experience**

The following adverse reactions have been identified during post-approval use of NEXIUM. 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 drug exposure.

Postmarketing Reports - There have been spontaneous reports of adverse events following postmarketing use of esomeprazole. These reports occurred rarely and are listed below by body system:

**Blood And Lymphatic System Disorders**: agranulocytosis, pancytopenia; *Eye Disorders*: blurring vision; *Gastrointestinal Disorders*: pancreatitis, stomatitis, microscopic colitis; *Gastrointestinal and/or Genitourinary Disorders*: hepatic failure, hepatitis with or without jaundice; *Immune System Disorders*: anaphylactic reaction/shock; *Integument System Disorders*: acute drug eruption/shock; *Neurologic Disorders*: cerebellar syndrome, toxic epidermal necrolysis (TEN, some fatal); *Respiratory System Disorders*: bronchiolitis obliterans organizing pneumonia; *Skin and Subcutaneous Tissue Disorders*: alopecia, erythema multiforme, urticaria, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN, some fatal), cutaneous lupus erythematosus.

Other adverse events not observed with NEXIUM, but occurring with omeprazole can be found in the omeprazole package insert. ADVERSE REACTIONS section.

**7 DRUG INTERACTIONS**

Esomeprazole is extensively metabolized in the liver by CYP2C19 and CYP3A4.

*In vitro and in vivo studies have shown that esomeprazole is not likely to inhibit CYPs 1A2, 2A6, 3A4, 2D6, 2E1 and 3A4. No clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. Drug interaction studies have shown that esomeprazole does not have any clinically significant interactions with phenytoin, warfarin, quinidine, clarithromycin or amoxicillin. Post-marketing reports of changes in prothrombin time have been reported after concomitant use of esomeprazole and warfarin. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time. Esomeprazole may potentially interfere with CYP2C19, the major esomeprazole metabolizing enzyme. Co-administration of esomeprazole 30 mg and dazepam, a CYP2C19 substrate, resulted in a 45% decrease in clearance of dazepam. Increased plasma levels of dazepam were observed 12 hours after dosing and onwards. However, at that time, the plasma levels of dazepam were below the therapeutic interval, and thus this interaction is unlikely to be of clinical relevance.*
Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of esomeprazole 40 mg results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition. Avoid concomitant administration of NEXIUM I.V. with clopidogrel. When using NEXIUM I.V., consider use of alternative anti-platelet therapy [see Clinical Pharmacology (12.3)].

Omeprazole acts as an inhibitor of CYP2C19. Omeprazole, given in doses of 40 mg daily for one week to 20 healthy subjects in cross-over, increased Cmax and AUC of cilostazol by 18% and 26%, respectively. Cmax and AUC of one of its active metabolites, 3,4-dihydroxy-cilostazol, which has 4-7 times the activity of cilostazol, were increased by 29% and 69%, respectively. Co-administration of clopidogrel with esomeprazole is expected to increase concentrations of cilostazol and its above mentioned active metabolite. Therefore, a dose reduction of cilostazol from 100 mg twice daily to 50 mg twice daily should be considered.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the omeprazole exposure. Dose adjustment of esomeprazole is not normally required for the recommended doses. However, in patients who may require higher doses, dose adjustment may be considered.

Data

Human Data

Esomeprazole is the S-isomer of omeprazole. Four epidemiological studies compared the frequency of congenital abnormalities among infants born to women who used omeprazole during pregnancy with the frequency of abnormalities among infants of women exposed to H2 receptor antagonists or other controls.

A population-based retrospective cohort study covering approximately 99% of all births in Sweden, 1998 to 2007, reported on 837,317 live births whose mothers did not use any proton pump inhibitor. The overall rate of birth defects in infants born to mothers with first trimester exposure to omeprazole was 2.9% and 2.6% in infants born to mothers not exposed to any proton pump inhibitor during the first trimester.

A retrospective cohort study reported on 689 pregnant women exposed to either H2-blockers or omeprazole in the first trimester (134 exposed to omeprazole) and 1,572 pregnant women unexposed to either during the first trimester. The overall malformation rate in offspring born to mothers with first trimester exposure to omeprazole, an H2-blocker, or were unexposed was 3.6%, 5.5%, and 4.1%, respectively.

A small prospective observational cohort study followed 113 women exposed to omeprazole during pregnancy (89% with first trimester exposures). The reported rate of major congenital malformations was 0.9% in the omeprazole-exposed group and 2.8% in the placebo group. The number of infants born with ventricular septal defects and the number of stillborn infants was slightly higher in the omeprazole-exposed infants than the expected number in this population.

Animal Data

Omeprazole

Reproductive studies conducted with omeprazole in rats at oral doses up to 138 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis) and in rabbits at doses up to 69.1 mg/kg/day (about 34 times an oral human dose of 40 mg on a body surface area basis) during organogenesis did not disclose any evidence for a teratogenic potential of omeprazole. In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (about 3.4 to 34 times an oral human dose of 40 mg on a body surface area basis) administered during organogenesis produced dose-related increases in embryo lethality, fetal resorptions, and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8 to 138.0 mg/kg/day (about 3.4 to 34 times an oral human dose of 40 mg on a body surface area basis), administered prior to mating through the lactation period.

Esomeprazole

No effects on embryo-fetal development were observed in reproduction studies with esomeprazole in rats (at oral doses up to 280 mg/kg/day) in rabbits at oral doses up to 86 mg/kg/day (about 41 times the human dose on a body surface area basis) administered during organogenesis.
For adult patients with bleeding gastric or duodenal ulcers and liver impairment, no dosage adjustment of the initial esomeprazole 80 mg infusion is necessary. For adult patients with mild to moderate liver impairment (Child-Pugh Classes A and B), a maximum continuous infusion of esomeprazole 6 mg/h should not be exceeded. For adult patients with severe liver impairment (Child-Pugh Class C), a maximum continuous infusion of 4 mg/h should not be exceeded [see Dosage and Administration (2.2), Clinical Pharmacology (12.3)].

10. OVERDOSAGE

The minimum lethal dose of esomeprazole sodium in rats after bolus administration was 310 mg/kg (about 75 times the human dose on a body surface area basis). The major signs of acute toxicity were reduced motor activity, changes in respiratory frequency, tremor, ataxia and intermittent clonic convulsions.

The symptoms described in connection with deliberate NEXIUM overdose (limited experience of doses in excess of 240 mg/day) are transient. Single oral doses of 80 mg and intravenous doses of 308 mg of esomeprazole over 24 hours were uneventful. Reports of overdosage with omeprazole in humans may also be relevant. Doses ranged up to 2,400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience (see omeprazole package insert - ADVERSE REACTIONS). No specific antidote for esomeprazole is known. Since esomeprazole is extensively protein bound, it is not expected to be removed by dialysis. In the event of overdose, treatment should be symptomatic and supportive. As with the management of any overdose, the possibility of multiple drug ingestion should be considered. For current information on treatment of any drug overdose, a certified Regional Poison Control Center should be contacted. Telephone numbers are listed in the Physicians’ Desk Reference (PDR) or local telephone book.

11. DESCRIPTION

The active ingredient in NEXIUM® I.V. (esomeprazole sodium) for Injection is (S)-5-methoxy-2-[4-[4-methoxy-3,5-dimethyl-2-pyridyl]-methyl][sulfanyl]-1 H-benzoimidazole sodium, a proton pump inhibitor that inhibits gastric acid secretion. Esomeprazole is the S-isomer of omeprazole, which is a mixture of the S- and R-isomers. Its empirical formula is C17H17N5O5Na with molecular weight of 367.4 g/mol (sodium salt) and 345.4 g/mol (parent compound). Esomeprazole sodium is very soluble in water and freely soluble in ethanol (95%). The structural formula is:

NEXIUM I.V. for Injection is supplied as a sterile, freeze-dried, white to off-white, porous cake or powder in a 5 mL vial, intended for intravenous administration after reconstitution with 0.9% Sodium Chloride Injection, USP; Lactated Ringer's Injection, USP or 5% Dextrose Injection, USP. NEXIUM I.V. for Injection contains esomeprazole sodium 21.3 mg or 42.5 mg equivalent to esomeprazole 20 mg or 40 mg, edetate disodium 1.5 mg and sodium hydroxide g.s. for pH adjustment. The pH of reconstituted solution of NEXIUM I.V. for Injection depends on the reconstitution volume and is in the pH range of 9 to 11. The stability of esomeprazole sodium in aqueous solution is strongly pH dependent. The rate of degradation increases with decreasing pH.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H+/K+-ATPase in the gastric parietal cell. The S- and R-isomers of omeprazole are protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulfenamide. By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity. This effect is dose-related up to a daily dose of 20 to 40 mg and leads to inhibition of gastric acid secretion.

12.2 Pharmacodynamics

Antisecretory Activity

The effect of intravenous esomeprazole on intragastric pH was determined in two separate studies. In the first study, 20 mg of NEXIUM I.V. for Injection was administered intravenously once daily at constant rate over 30 minutes for 5 days. Twenty-two healthy subjects were included in the study. In the second study, 40 mg of NEXIUM I.V. for Injection was administered intravenously once daily at constant rate over 30 minutes for 5 days. Thirty-eight healthy subjects were included in the study.

Table 4: Effect of NEXIUM I.V. for Injection on Intragastric pH on Day 5

<table>
<thead>
<tr>
<th></th>
<th>Esomeprazole 20 mg (n=22)</th>
<th>Esomeprazole 40 mg (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Time Gastric pH&lt;4</td>
<td>49.5</td>
<td>66.2</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>41.9–57.2</td>
<td>62.4–70.0</td>
</tr>
</tbody>
</table>

Gastric pH was measured over a 24-hour period in a study in H. pylori negative healthy Caucasian volunteers (n=24), the % time over 24 hours (95% CI) when intragastric pH was < 4 was 52.3% (40.3 – 64.4) and 4.8 % (1.8 – 7.8), respectively during administration of esomeprazole as an intravenous infusion of 80 mg over 30 minutes followed by a continuous infusion of 8 mg/h for 23.5 hours.

8.4 Pediatric Use

The safety and effectiveness of NEXIUM I.V. for Injection have been established in pediatric patients 1 month to 17 years of age for short-term treatment of GERD with Erosive Esophagitis [see Clinical Pharmacology (12.3)]. However, effectiveness has not been established in patients less than 1 month of age.

1 month to 17 years of age

Use of NEXIUM I.V. for Injection in pediatric patients 1 month to 17 years of age for short-term treatment of GERD with Erosive Esophagitis is supported by: a) results observed from a pharmacokinetic (PK) study on NEXIUM I.V. for Injection performed in pediatric patients, b) predictions from a population PK model comparing I.V. PK data between adult and pediatric patients, and c) relationship between exposure and pharmacodynamic results obtained from adult I.V. and pediatric oral data and d) PK results already included in the current approved labeling and from adequate and well-controlled studies that supported the approval of NEXIUM I.V. for Injection for adults.

Neonates 0 to 1 month of age

Following administration of NEXIUM I.V. in neonates the geometric mean (range) for CL was 0.17 L/h/kg (0.04 L/h/kg–0.32 L/h/kg). The safety and effectiveness of NEXIUM I.V. in neonates have not been established.

Juvenile Animal Data

In a juvenile rat toxicity study, esomeprazole was administered with both magnesium and strontium salts at oral doses of about 34 to 68 times a daily human dose of 40 mg based on body surface area. Increases in death were seen at the high dose, and at all doses of esomeprazole, there were decreases in body weight, body weight gain, femur weight and femur length, and decreases in overall growth [see Nonclinical Toxicology (13.2)].

8.5 Geriatric Use

Of the total number of patients who received oral NEXIUM in clinical trials, 1,459 were 74 to 84 years of age and 354 patients were ≥ 75 years of age.

No overall differences in safety and efficacy were observed between the elderly and younger individuals, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

For adult patients with GERD, no dosage adjustment is necessary in patients with mild to moderate hepatic insufficiency (Child-Pugh Classes A and B). For patients with severe hepatic insufficiency (Child-Pugh Class C) a dose of 20 mg once daily should not be exceeded [see Dosage and Administration (2), Clinical Pharmacology (12.3)].
In a study in H. pylori positive and H. pylori negative healthy Chinese subjects (overall n=19), the % time over 24 hours (95% CI) when intragastric pH was > 6 and > 7 was 53% (45.6 – 60.3) and 15.1% (9.5 – 20.7) in the overall study population during administration of esomeprazole as an intravenous infusion of 80 mg over 30 minutes followed by a continuous infusion of 8 mg/h for 23.5 hours. When comparing H. pylori positive (n=8) vs. negative (n=11) subjects, the percentage of time in a 24 hour period with intragastric pH > 6 (59% vs. 47 %) and with > 7 (17% vs. 11 %) tended to be larger in the H. pylori positive subjects.

Esomeprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system. The metabolites of esomeprazole lack antisecretory activity. The major part of esomeprazole’s metabolism is dependent upon the CYP2C19 isoenzyme, which forms the hydroxy and desmethyl metabolites. The remaining amount is dependent on CYP3A44 which forms the sulphone metabolite. CYP2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole, since some 3% of Caucasians and 15-20% of Asians lack CYP2C19 and are termed Poor Metabolizers. At steady state, the ratio of AUC in Poor Metabolizers to AUC in the rest of the population (Extensive metabolizers) is approximately 2. Following administration of equinolar doses, the S- and R-isomers are metabolized differently by the liver, resulting in higher plasma levels of the S- than of the R-isomer.

Excretion
Esomeprazole is excreted as metabolites primarily in urine but also in feces. Less than 1% of parent drug is excreted in the urine. Esomeprazole is completely eliminated from plasma, and there is no accumulation during once daily administration. The plasma elimination half-life of intravenous esomeprazole is approximately 1.1 to 1.4 hours and is prolonged with increasing dose of intravenous esomeprazole. During administration of esomeprazole once 24 hours as an intravenous infusion of 80 mg over 30 minutes followed by a continuous infusion of 8 mg/h for 23.5 hours plasma clearance (CL) is approximately 5.9 to 7.2 L/h.

Concomitant Use with Clopidogrel
Results from a crossover study in healthy subjects have shown a pharmacokinetic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. once daily) when co-administered for 30 days. Exposure to the active metabolite of clopidogrel was reduced by 35% to 40% over this time period. Pharmacodynamic parameters were also reduced by 30–40% and demonstrated a time-dependent increase in platelet aggregation was related to the change in the exposure to clopidogrel active metabolite.

Concomitant Use with Mycophenolate Mofetil
Administration of mycophenolate mofetil (MPA) 1000 mg twice daily for 4 days and a single 1000 mg dose of MMF approximately one hour after the last dose of mycophenolate to 12 healthy subjects in a crossover study resulted in a 52% reduction in the Cmax and 23% reduction in the AUC of MPA.

Specific Populations
Investigation of age, gender, race, renal, and hepatic impairment and metabolizer status has been made previously with oral esomeprazole. The pharmacokinetics of esomeprazole is not expected to be affected differently by intrinsic or extrinsic factors after intravenous administration compared to oral administration. The same recommendations for dose adjustment in special populations are suggested for intravenous esomeprazole as for oral esomeprazole.

Age: Geriatric Population
In oral studies, the AUC and Cmax values were slightly higher (25% and 18%, respectively) in the elderly as compared to younger subjects at steady state. Dosage adjustment based on age is not necessary.

Age: Pediatric Population
In a randomized, open-label, multi-national, repeated dose study, esomeprazole PK was evaluated following a once-daily 3-minute injection in a total of 50 pediatric patients 0 to 17 years old, inclusive. Esomeprazole plasma AUC values for 20 mg NEXIUM IV were 183% and 60% higher in pediatric patients aged 6 – 11 years and 12 – 17 years respectively compared to adults given 20 mg. Subsequent pharmacokinetic analyses predicted that a dose of 0.5 mg/kg once-daily for pediatric patients 1-11 months of age, 10 mg for pediatric patients 1-7 years with body weight ≥55 kg, and 20 mg for pediatric patients 7-17 years with body weight ≥55 kg would achieve comparable steady-state plasma exposures (AUC,0-24) to those observed in adult patients administered 20 mg of NEXIUM I.V. once every 24 hours. Further, increasing the infusion duration from 3 minutes to 10 minutes or 30 minutes was predicted to produce steady-state Cmax values that were comparable to those observed in adult patients at the 40 mg and 20 mg NEXIUM I.V. doses.

Hepatic Impairment
In oral studies, the steady state pharmacokinetics of esomeprazole obtained after administration of 40 mg once daily to 4 patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B), and severe (Child-Pugh Class C) liver insufficiency were compared to those obtained in 36 male and female GERD patients with normal liver function. In patients with mild and moderate hepatic insufficiency, the AUCs were within the range that could be expected in patients with normal liver function. In patients with severe hepatic insufficiency the AUCs were 2 to 3 times higher than in the patients with normal liver function. No dosage adjustment is recommended for patients with mild to moderate hepatic insufficiency (Child-Pugh Classes A and B). However, in patients with severe hepatic insufficiency (Child-Pugh Class C) a maximum dose of 20 mg once daily should not be exceeded (see Dosage and Administration [2]. Use in Specific Populations [8.6]).

There are no pharmacokinetic data available for esomeprazole administered as continuous intravenous administration in patients with liver impairment. The pharmacokinetics of esomeprazole 80 mg over 30 minutes, followed by 8 mg/h over 23.5 hours, systemic esomeprazole exposures were modestly higher (+17%) in the CYP2C19 intermediate metabolizers (M; n=6) compared to extensive metabolizers (EM; n=17) of CYP2C19. Similar PK differences were noted across these genotypes in a Chinese healthy volunteer study that included 7 EMs and 11 IMs. There is very limited PK information for poor metabolizers (PM) from these studies.

In adults with bleeding gastric or duodenal ulcers and liver impairment, no dosage adjustment of the initial esomeprazole 80 mg infusion is necessary. For adults with mild to moderate liver impairment (Child-Pugh Classes A and B), a maximum continuous infusion of esomeprazole 6 mg/h should not be exceeded. For adult patients with severe liver

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NEXIUM I.V. 20 mg</th>
<th>NEXIUM I.V. 40 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (µmol/h/L)</td>
<td>(3.96:6.61)</td>
<td>(14.46:18.16)</td>
</tr>
<tr>
<td>Cmax (µmol/L)</td>
<td>3.86</td>
<td>7.51</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>(3.16:4.72)</td>
<td>(6.93:8.13)</td>
</tr>
<tr>
<td>(0.90:1.22)</td>
<td>(1.05)</td>
<td>(1.41)</td>
</tr>
</tbody>
</table>

Values represent the geometric mean (95% CI) during administration of esomeprazole over 24 hours as an intravenous infusion of 80 mg over 30 minutes followed by a continuous infusion of 8 mg/h for 23.5 hours (for a total of 24 hours) in healthy volunteers (n=24), esomeprazole PK parameters (geometric mean value (95% CI)) were as follows: AUC, 111.1 µmol·h/L (100.5-122.7 µmol·h/L), Cmax, 15.0 µmol/L (13.5-16.6 µmol/L), and steady state plasma concentration (Css) 3.9 µmol/L (3.0-4.5 µmol/L). In a Caucasian healthy volunteer study evaluating esomeprazole 80 mg over 30 minutes, followed by 8 mg/h over 23.5 h, systemic esomeprazole exposures were modestly higher (+17%) in the CYP2C19 intermediate metabolizers (M; n=6) compared to extensive metabolizers (EM; n=17) of CYP2C19. Similar PK differences were noted across these genotypes in a Chinese healthy volunteer study that included 7 EMs and 11 IMs. There is very limited PK information for poor metabolizers (PM) from these studies.
impairment (Child-Pugh Class C), a maximum continuous infusion of 4 mg/h should not be exceeded [see Dosage and Administration (2.2), Use in Specific Populations (8.6)].

12.4 Microbiology

Effects on Gastrointestinal Microbial Ecology

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 hospitalized patients, possibly also Clostridium difficile.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of esomeprazole was assessed using omeprazole studies. In two 24-month oral carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0, and 140.8 mg/kg/day (about 0.4 to 34 times the human dose of 40 mg/day expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 3.4 times the human dose of 40 mg/day on a body surface area basis) for 1 year, then followed for an additional year without the drug. No carcinoids were seen in these rats. A greater incidence of treatment-related ECL cell hyperplasia was observed at the end of 1 year (94% treated vs 10% control). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for 2 years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. A 78-week oral mouse carcino genesis study of omeprazole did not show increased tumor occurrence, but the study was not conclusive. Omeprazole was negative in the Ames mutation test, in the in vitro bone marrow cell chromosome aberration test, and the in vivo mouse micronucleus test. Omeprazole, however, was positive in the in vitro mouse lymphocyte chromosome aberration test. Omeprazole was positive in the in vitro mouse lymphocyte chromosome aberration test, the in vivo mouse bone marrow cell chromosome aberration test, and the in vivo mouse micronucleus test. The potential effects of esomeprazole on fertility and reproductive performance were assessed using omeprazole studies. Omeprazole at oral doses up to 138 mg/kg/day in rats (about 34 times the human dose of 40 mg/day on a body surface area basis) was found to have no effect on reproductive performance of parental animals.

13.2 Animal Toxicology and/or Pharmacology

Reproduction Studies

Reproduction studies have been performed in rats at oral doses up to 280 mg/kg/day (about 68 times an oral human dose of 40 mg on a body surface area basis) and in rabbits at oral doses up to 85 mg/kg/day (about 42 times an oral human dose of 40 mg on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to esomeprazole [see Use in Specific Populations (8.1)].

Juvenile Animal Study

A 28-day toxicity study with a 14-day recovery phase was conducted in juvenile rats with esomeprazole magnesium at doses of 70 to 280 mg/kg/day (about 17 to 68 times a daily oral human dose of 40 mg on a body surface area basis). An increase in the number of deaths at the high dose of 280 mg/kg/day was observed when juvenile rats were administered esomeprazole magnesium from postnatal day 7 through postnatal day 35. In addition, doses equal to or greater than 140 mg/kg/day (about 34 times a daily oral human dose of 40 mg on a body surface area basis), produced treatment-related decreases in body weight (approximately 14%) and body weight gain, decreases in femur weight and femur length, and affected overall growth. Comparable findings described above have also been observed in this study with another esomeprazole salt, esomeprazole strontium, at equimolar doses of esomeprazole.

14 CLINICAL STUDIES

14.1 Acid Suppression in Gastroesophageal Reflux Disease (GERD)

Four multicenter, open-label, two-period crossover studies were conducted to compare the pharmacodynamic efficacy of the intravenous formulation of esomeprazole (20 mg and 40 mg) to that of NEXIUM delayed-release capsules at corresponding doses in patients with symptoms of GERD, with or without erosive esophagitis. The patients (n=206, 18 to 72 years old; 112 female, 110 Caucasian, 50 Black, 10 Asian, and 36 Other Race) were randomized to receive either 20 or 40 mg of intravenous or oral esomeprazole once daily for 10 days (Period 1), and then were switched in Period 2 to the other formulation for 10 days, matching their respective dose level from Period 1. The intravenous formulation was administered as a 3-minute injection in two of the studies, and as a 15-minute infusion in the other two studies. Basal acid output (BAO) and maximal acid output (MAO) were determined 22-24 hours post-dose on Period 1, Day 11; on Period 2, Day 3; and on Period 2, Day 11. BAO and MAO were estimated using a 2-hour continuous collections of gastric contents prior to and following (respectively) subcutaneous injection of 6.0 mcg/kg of pentagastrin. In these studies, after 10 days of once daily administration, the intravenous dosage forms of NEXIUM 20 mg and 40 mg were similar to the corresponding oral dosage forms in their ability to suppress BAO and MAO in these GERD patients (see table below).

There were no major changes in acid suppression when switching between intravenous and oral dosage forms.

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose</th>
<th>Intravenous Administration Method</th>
<th>BAO in mmol H⁺/h</th>
<th>MAO in mmol H⁺/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>15-minute infusion</td>
<td>0.71 (1.24)</td>
<td>0.69 (1.24)</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>15-minute infusion</td>
<td>0.78 (1.38)</td>
<td>0.82 (1.34)</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>3-minute injection</td>
<td>0.36 (0.61)</td>
<td>0.31 (0.55)</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>15-minute infusion</td>
<td>0.36 (0.79)</td>
<td>0.22 (0.39)</td>
</tr>
</tbody>
</table>