Nexicure

Esomeprazole 2.5, 5, 10 and 20 mg

Enteric Coated Granules for Delayed Release Oral Suspension

1 Composition

Each nexicure 2.5 mg enteric coated granules for delayed release oral suspension contains:

29.413 mg Esomeprazole Magnesium Trihydrate 8.5% MUPs equivalent to 2.5 mg Esomeprazole

Each nexicure 5 mg enteric coated granules for delayed release oral suspension contains:

58.83 mg Esomeprazole Magnesium Trihydrate 8.5% MUPs equivalent to 5 mg Esomeprazole

Each nexicure 10 mg enteric coated granules for delayed release oral suspension contains:

117.65 mg Esomeprazole Magnesium Trihydrate 8.5% MUPs equivalent to 10 mg Esomeprazole

Each nexicure 20 mg enteric coated granules for delayed release oral suspension contains:

235.3 mg Esomeprazole Magnesium Trihydrate 8.5% MUPs equivalent to 20 mg Esomeprazole

Excipients:

Maltodextrin, Citric acid anhydrous, Sucralose, Quinoline Yellow (C.I.No: 47005), Xanthan gum, Strawberry dry flavor, Colloidal silicon dioxide (Aerosil 200), Povidone K30, Isopropyl alcohol

2 INDICATIONS AND USAGE

2.1 Healing of Erosive Esophagitis (EE)

Central Administration for Pharmaceutical care Approval Date: 3/11 /2022 1st Revisor: Dr/Shaza
General Administration of Scientific Reference and Medical Inserts
Medical Inserts Administration According to: FDA

Adults

NEXICURE for enteric coated granules for delayed release oral suspension are indicated for the short-term treatment (4 to 8 weeks) in the healing and symptomatic resolution of diagnostically confirmed EE in adults. For those patients who have not healed after 4 to 8 weeks of treatment, an additional 4- to 8- week course of NEXICURE may be considered.

Pediatric Patients 12 Years to 17 Years of Age

NEXICURE for enteric coated granules for delayed release oral suspension are indicated for the short-termtreatment (4 to 8 weeks) for the healing of EE in pediatric patients 12 years to 17 years of age.

Pediatric Patients 1 Year to 11 Years of Age

NEXICURE for enteric coated granules for delayed release delayed release oral suspension is indicated for the short-term treatment (8 weeks) for the healing of EE in pediatric patients 1 year to 11 years of age.

Pediatric Patients 1 Month to Less Than 1 Year of Age

NEXICURE for enteric coated granules for delayed release oral suspension is indicated for short-term treatment (up to 6 weeks) of EE due to acid-mediated GERD in pediatric patients 1 month to less than 1 year of age.

2.2 Maintenance of Healing of EE

NEXICURE for delayed-release oral suspension are indicated for the maintenance of healing of EE in adults. Controlled studies do not extend beyond 6 months.

2.3 Treatment of Symptomatic GERD

Adults

NEXICURE for enteric coated granules for delayed release oral suspension are indicated for short-termtreatment (4 to 8 weeks) of heartburn and other symptoms associated with GERD in adults.

Dr/Sha 3/11/2022

Pediatric Patients 12 Years to 17 Years of Age

NEXICURE for enteric coated granules for delayed release oral suspension are indicated for short-term treatment (4 weeks) of heartburn and other symptoms associated with GERD in pediatric patients 12 years to 17 years of age.

Pediatric Patients 1 Year to 11 Years of Age

NEXICURE for enteric coated granules for delayed release oral suspension is indicated for short-term treatment (up to 8 weeks) of heartburn and othersymptoms associated with GERD in pediatric patients 1 year to 11 years of age.

2.4 Risk Reduction of Nonsteroidal Anti-Inflammatory Drugs (NSAID)-Associated Gastric Ulcer

NEXICURE for enteric coated granules for delayed release oral suspension are indicated for the reduction in the occurrence of gastric ulcers associated with continuous NSAID therapy in adult patients at risk for developing gastric ulcers. Patients are considered to be at risk due to their age (60 years and older) and/or documented history of gastriculcers. Controlled studies do not extend beyond 6 months.

2.5 *Helicobacter pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence

Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

Triple Therapy

NEXICURE for enteric coated granules for delayed release oral suspension in combination with amoxicillin and clarithromycin is indicated for the treatment of adult patients with *H. pylori* infection and duodenal ulcer disease (active orhistory of within the past 5 years) to eradicate *H. pylori*.

In patients who fail therapy, susceptibility testing should be done. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative

Central Administration for Pharmaceutical care Approval Date: 3/11 /2022 1st Revisor: Dr/Shaza
General Administration of Scientific Reference and Medical Inserts
Medical Inserts Administration According to: FDA

antimicrobial therapy should be instituted.

2.6 Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

NEXICURE for enteric coated granules for delayed release oral suspension are indicated for the long-termtreatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome, in adults.

3 DOSAGE AND ADMINISTRATION

3.1 Recommended Dosage in Adults by Indication

Table 1 shows the recommended adult dosage of NEXICURE by indication.
The duration of NEXICURE treatment should be based on available safety and efficacy data specific to the defined indication and dosing frequency and individual patient medical needs. NEXICURE should only be initiated and continued if the benefits outweigh the risks of treatment.

Table 1: Recommended Dosage of NEXICURE in Adults by Indication

Adult Indication	Recommended Dosage of NEXICURE for enteric coated granules for delayed release oral suspension	Treatment Duration
Healing of EE	20 mg or 40 mg[1] once daily	4 to 8 weeks[2]
Maintenance of Healing of EE	20 mg once daily	Controlled studies do not extend beyond 6months
Treatment of Symptomatic GERD	20 mg once daily	4 weeks; if symptoms do not resolve completely, consider an additional 4 weeks
Risk Reduction of NSAID-Associated GastricUlcer	20 mg or 40 mg[1] once daily	Controlled studies donot extend beyond 6 months
H. pylori	NEXICURE 40 mg once daily[1]	10 days

Eradication to Reduce the Risk of Duodenal Ulcer Recurrence (Triple Therapy)	Amoxicillin 1000 mg twice daily[3]	10 days
	Clarithromycin 500 mg twice daily[3]	10 days
Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome	Starting dosage is 40 mg twice daily[4]; individualize the regimen to patient needs. Dosages of up to 240 mg/day have been administered	As long as clinically indicated

[1] A maximum dosage of 20 mg once daily is recommended for patients with severe liver impairment (Child-Pugh Class C)

[2] Most patients are healed within 4 to 8 weeks. For patients who do not heal after 4 to 8 weeks, an additional 4 to 8 weeks oftreatment may be required to achieve healing.

[3] Refer to the amoxicillin and clarithromycin prescribing information for dosage adjustments in elderly and renally-impairedpatients.

[4] A starting dosage of 20 mg twice daily is recommended for patients with severe liver impairment (Child-Pugh Class C).

3.2 Recommended Dosage in Pediatric Patients by Indication

Table 2 shows the recommended dosage of NEXICURE in pediatric patients by indication.

Table 2: Recommended Dosage of NEXICURE in Pediatric Patients by Indication

Indication	Patient Age	Recommended Dosage	Duration
	12 years to 17 years	NEXICURE for enteric coated granules for delayed release oral suspension: 20 mg or 40 mg once daily	4 to 8 Weeks

Central Administration for Pharmaceutical care Approval Date: 3/11 /2022 1st Revisor: Dr/Shaza
General Administration of Scientific Reference and Medical Inserts
Medical Inserts Administration According to: FDA

Healing of EE	1 year to 11 years[1]	NEXICURE for enteric coated granules for delayed release oral suspension: <u>Less than 20 kg</u> 10 mg once daily <u>20 kg and greater</u> 10 mg or 20 mg once daily	8 weeks
Treatment of EE due to Acid-Mediated GERD	1 month to less than 1 year[2]	NEXICURE for enteric coated granules for delayed release oral suspension: <u>3 kg to 5 kg</u> 2.5 mg once daily <u>Greater than 5 kg to 7.5 kg</u> 5 mg once daily <u>Greater than 7.5 kg to 12 kg</u> 10 mg once daily	Up to 6 weeks
Treatment of Symptomatic GERD	12 years to 17 years	NEXICURE for enteric coated granules for delayed release oral suspension: 20 mg once daily	4 weeks
	1 year to 11 years	NEXICURE for enteric coated granules for delayed release oral suspension: 10 mg once daily[1]	Up to 8 weeks

[1] Dosages over 1 mg/kg/day have not been studied

[2] Dosages over 1.33 mg/kg/day have not been studied

3.3 Preparation and Administration Instructions

- Take NEXICURE for enteric coated granules for delayed release oral suspension at least one hour before meals.
- Antacids may be used concomitantly with NEXICURE.
- Take a missed dose as soon as possible. If it is almost time for the next dose, skip the missed dose and take thenext dose at the regular scheduled time. Do not

take 2 doses at the same time.

NEXICURE for Enteric Coated Granules for delayed release Oral Suspension

Administer NEXICURE for enteric coated granules for delayed release oral suspension orally or via a nasogastric or gastric tube, as described below.

Oral Administration

1. Empty the contents of a 2.5 mg or 5 mg NEXICURE packet into a container containing 5 mL of water. For the 10 mg, and 20 mg strengths, the contents of a packet should be emptied into a container containing 15 mL of water.If two packets are needed, mix in a similar way add twice the required amount of water.
2. Stir the packet contents into the water.
3. Leave 2 to 3 minutes to thicken.
4. Stir and drink within 30 minutes.
5. If any of the contents remain after drinking, add more water, stir, and drink immediately.

Administration via Nasogastric or Gastric Tube

1. Add 5 mL of water to a catheter-tipped syringe and then add the contents of a 2.5 mg or 5 mg NEXICURE packet. For the 10 mg, and 20 mg packet strengths, add at least 15 mL of water to the catheter-tipped syringe.
2. Immediately shake the catheter-tipped syringe and leave 2 to 3 minutes to thicken.
3. Shake the catheter-tipped syringe and inject through the nasogastric or gastric tube, French size 6 or larger, into thestomach within 30 minutes.
4. Refill the catheter-tipped syringe with an equal amount of water (5 mL or 15 mL).
5. Shake and flush any remaining contents from the nasogastric or gastric tube into the stomach.

4 DOSAGE FORMS AND STRENGTHS

Central Administration for Pharmaceutical care Approval Date: 3/11 /2022 1st Revisor: Dr/Shaza
General Administration of Scientific Reference and Medical Inserts
Medical Inserts Administration According to: FDA

NEXICURE Enteric Coated Granules for Delayed Release Oral Suspension

- 2.5 mg, 5 mg, 10 mg, and 20 mg esomeprazole in unit dose packets containing Pale yellow to yellow fine granules give pale yellow to yellow suspension.

5 CONTRAINDICATIONS

- NEXICURE 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, bronchospasm, acute tubulointerstitial nephritis, and urticaria.
- For information about contraindications of amoxicillin and clarithromycin, indicated in combination with NEXICURE for *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence, refer to the Contraindications sectionof the respective prescribing information.
- Proton pump inhibitors (PPIs), including NEXICURE, are contraindicated in patients receiving rilpivirinecontaining products.

6 WARNINGS AND PRECAUTIONS

6.1 Presence of Gastric Malignancy

In adults, symptomatic response to therapy with NEXICURE does not preclude the presence of gastric malignancy. Consideradditional follow-up and diagnostic testing in adult patients who have a suboptimal response or an early symptomatic relapse after completing treatment with a PPI. In older patients, also consider an endoscopy.

6.2 Acute Tubulointerstitial Nephritis

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking PPIs and may occur at any point during PPItherapy. Patients may present with varying signs and symptoms from symptomatic hypersensitivity reactions to non-specific symptoms of decreased renal function (e.g., malaise, nausea, anorexia). In reported case series, some

patients were diagnosed on biopsy and in the absence of extra-renal manifestations (e.g., fever, rash or arthralgia). Discontinue NEXICURE and evaluate patients with suspected acute TIN.

6.3 *Clostridium difficile*-Associated Diarrhea

Published observational studies suggest that PPI therapy like NEXICURE may be associated with an increased risk of *Clostridium difficile*-associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve.

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

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents. For more information specific to antibacterial agents (clarithromycin and amoxicillin) indicated for use in combination with NEXICURE, refer to Warnings and Precautions section of the corresponding prescribing information.

6.4 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.

6.5 Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS)

Central Administration for Pharmaceutical care Approval Date: 3/11 /2022 1st Revisor: Dr/Shaza
General Administration of Scientific Reference and Medical Inserts
Medical Inserts Administration According to: FDA

and toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematouspustulosis (AGEP) have been reported in association with the use of PPIs.
Discontinue NEXICURE at the first signs or symptoms of severe cutaneous adverse reactions or other signs ofhypersensitivity and consider further evaluation.

6.6 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 autoimmunedisease. 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 (SCLE) and occurred withinweeks 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 SLEis 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 NEXICURE, 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.

6.7 Interaction with Clopidogrel

Avoid concomitant use of NEXICURE with clopidogrel. Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is entirely due to an active metabolite. The metabolism of clopidogrel to its active metabolite can be impairedby use with concomitant medications, such as esomeprazole, that inhibit CYP2C19 activity. Concomitant use of clopidogrel with 40 mg esomeprazole reduces the pharmacological activity of clopidogrel. When using NEXICURE consider alternative anti-platelet therapy.

6.8 Cyanocobalamin (Vitamin B-12) Deficiency

Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead tomalabsorption of cyanocobalamin (vitamin B-12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

6.9 Hypomagnesemia and Mineral Metabolism

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least threemonths, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures.
Hypomagnesemia may lead to hypocalcemia and/or hypokalemia and may exacerbate underlying hypocalcemia in at-riskpatients. 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 maycause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically.

Consider monitoring magnesium and calcium levels prior to initiation of NEXICURE and periodically while on treatment inpatients with a preexisting risk of hypocalcemia (e.g.,

Central Administration for Pharmaceutical care Approval Date: 3/11 /2022 1st Revisor: Dr/Shaza
General Administration of Scientific Reference and Medical Inserts
Medical Inserts Administration According to: FDA

hypoparathyroidism). Supplement with magnesium and/or calcium, as necessary. If hypocalcemia is refractory to treatment, consider discontinuing the PPI.

6.10 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 esomeprazoleconcentrations. Avoid concomitant use of NEXICURE with St. John's Wort or rifampin.

6.11 Interactions with Diagnostic Investigations for Neuroendocrine Tumors

Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgAlevel may cause false positive results in diagnostic investigations for neuroendocrine tumors. Healthcare providers shouldtemporarily 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.

6.12 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 metabolite, possibly leading to methotrexatetoxicities. In high-dose methotrexate administration a temporary withdrawal of the PPI may be considered in some patients.

6.13 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.

7 ADVERSE REACTIONS

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

- Acute Tubulointerstitial Nephritis
- *Clostridium difficile*-Associated Diarrhea
- Bone Fracture
- Severe Cutaneous Adverse Reactions
- Cutaneous and Systemic Lupus Erythematosus
- Cyanocobalamin (Vitamin B-12) Deficiency
- Hypomagnesemia and Mineral Metabolism
- Fundic Gland Polyps

8 Post marketing Experience:

The following adverse reactions have been identified during post-approval use of esomeprazole. 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. These reports are listed below by body system:

-*Blood and Lymphatic:* agranulocytosis, pancytopenia.
-*Eye:* blurred vision.
-*Gastrointestinal:* pancreatitis; stomatitis; microscopic colitis; fundic gland polyps.
-*Hepatobiliary:* hepatic failure, hepatitis with or without jaundice.
-*Immune System:* anaphylactic reaction/shock; systemic lupus erythematosus.
-*Infections and Infestations:* GI candidiasis; *Clostridium difficile*-associated diarrhea.
-***Metabolism and nutritional disorders:*** **hypomagnesemia (may lead to hypocalcemia and/or hypokalemia).**
-*Musculoskeletal and Connective Tissue:* muscular weakness, myalgia, **bone fracture.**

Central Administration for Pharmaceutical care Approval Date: 3/11 /2022 1st Revisor: Dr/Shaza
General Administration of Scientific Reference and Medical Inserts
Medical Inserts Administration According to: FDA

-*Nervous System:* hepatic encephalopathy, taste disturbance.
-*Psychiatric:* aggression, agitation, depression, hallucination.
-*Renal and Urinary:* interstitial nephritis.
-*Reproductive System and Breast:* gynecomastia.
-*Respiratory, Thoracic, and Mediastinal:* bronchospasm.
-***Skin and Subcutaneous Tissue:*** **alopecia, erythema multiforme, hyperhidrosis, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal), drug reaction with eosinophilia and systemic symptoms (DRESS), andacute generalized exanthematous pustulosis (AGEP), cutaneous lupus erythematosus.**

Adverse reactions associated with omeprazole may also be expected to occur with esomeprazole. See the full prescribing information for omeprazole for complete safety information.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via

The Egyptian Pharmacovigilance Center:

Address: 21 Abd El Aziz Al Soud Street, El-Manial, Cairo, Egypt, And PO Box: 11451
Telephone: (+2) 02 25354100, Extension: 1303
Fax: +202 – 23610497
Email: pv.followup@edaegypt.gov.eg

Or Zeta pharma PV Email: pv@zeta-pharma.com

9 DRUG INTERACTIONS

Tables 3 and 4 include drugs with clinically important drug interactions and interaction with diagnostics when administered concomitantly with esomeprazole and instructions for preventing or managing them.

Consult the labeling of concomitantly used drugs to obtain further information about

interactions with PPIs.

Table 3: Clinically Relevant Interactions Affecting Drugs Co-Administered with Esomeprazole andInteraction with Diagnostics

Antiretrovirals	
Clinical Impact:	The effect of PPIs on antiretroviral drugs is variable. The clinical importance and themechanisms behind these interactions are not always known. • Decreased exposure of some antiretroviral drugs (e.g., rilpivirine atazanavir, andnelfinavir) when used concomitantly with esomeprazole may reduce antiviral effect and promote the development of drug resistance. • Increased exposure of other antiretroviral drugs (e.g., saquinavir) when usedconcomitantly with esomeprazole may increase toxicity. • There are other antiretroviral drugs which do not result in clinically relevantinteractions with esomeprazole.
Intervention:	Rilpivirine-containing products: Concomitant use with NEXICURE is contraindicated. Atazanavir: See prescribing information for atazanavir for dosing information. Nelfinavir: Avoid concomitant use with NEXICURE. See prescribing information fornelfinavir. Saquinavir: See the prescribing information for saquinavir for monitoring of potentialsaquinavir-related toxicities. Other antiretrovirals: See prescribing information for specific antiretroviral drugs
Warfarin	
Clinical Impact:	Increased INR and prothrombin time in patients receiving PPIs, including esomeprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormalbleeding and even death.
Intervention:	Monitor INR and prothrombin time and adjust the dose of warfarin, if needed, tomaintain the target INR range.
Methotrexate	
Clinical Impact:	Concomitant use of esomeprazole with methotrexate (primarily at high dose) mayelevate and prolong serum concentrations of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities. No formal drug interaction studies of high-dose methotrexate with PPIs have been conducted.

Central Administration for Pharmaceutical care Approval Date: 3/11 /2022 1st Revisor: Dr/Shaza
General Administration of Scientific Reference and Medical Inserts
Medical Inserts Administration According to: FDA

Intervention:	A temporary withdrawal of NEXICURE may be considered in some patients receivinghigh-dose methotrexate.
2C19 Substrates (e.g., clopidogrel, citalopram, cilostazol)	
Clopidogrel	
Clinical Impact:	Concomitant use of esomeprazole 40 mg resulted in reduced plasma concentrations ofthe active metabolite of clopidogrel and a reduction in platelet inhibition. There are no adequate combination studies of a lower dose of esomeprazole or a higherdose of clopidogrel in comparison with the approved dose of clopidogrel.
Intervention:	Avoid concomitant use with NEXICURE Consider use of alternative anti-platelet therapy.
Citalopram	
Clinical Impact:	Increased exposure of citalopram leading to an increased risk of QT prolongation..
Intervention:	Limit the dose of citalopram to a maximum of 20 mg per day. See prescribinginformation for citalopram.
Cilostazol	
Clinical Impact:	Increased exposure of cilostazol and one of its active metabolites (3,4-dihydro-cilostazol).
Intervention:	Consider reducing the dose of cilostazol from 100 mg twice daily to 50 mg twice daily. See prescribinginformation for cilostazol.
Digoxin	
Clinical Impact:	Potential for increased exposure of digoxin.
Intervention:	Monitor digoxin concentrations and adjust the dose, if needed, to maintain therapeuticdrug concentrations. See prescribing information for digoxin.
Combination Therapy with Clarithromycin and Amoxicillin	
Clinical Impact:	Concomitant administration of clarithromycin with other drugs can lead to seriousadverse reactions, including potentially fatal arrhythmias, and are contraindicated. Amoxicillin also has drug interactions.
Intervention:	See *Contraindications*, *Warnings* and *Precautions* in prescribing information forclarithromycin. See *Drug Interactions* in prescribing information for amoxicillin.
Drugs Dependent on Gastric pH for Absorption (e.g., iron salts, erlotinib, dasatinib, nilotinib,mycophenolate mofetil, ketoconazole/itraconazole)	
Clinical Impact:	Esomeprazole can reduce the absorption of other drugs due to its effect on reducing intragastric acidity

Intervention:	Mycophenolate mofetil (MMF): Co-administration of omeprazole, of which esomeprazole is an enantiomer, in healthy subjects and in transplant patients receivingMMF has been reported to reduce the exposure to the active metabolite, mycophenolicacid (MPA), possibly due to a decrease in MMF solubility at an increased gastric pH. The clinical relevance of reduced MPA exposure on organ rejection has not been established in transplant patients receiving NEXICURE and MMF. Use NEXICURE with caution in transplant patients receiving MMF. See the prescribing information for other drugs dependent on gastric pH for absorption.
Tacrolimus	
Clinical Impact:	Potentially increased exposure of tacrolimus, especially in transplant patients who areintermediate or poor metabolizers of CYP2C19.
Intervention:	Monitor tacrolimus whole blood concentrations and consider reducing the dose, if needed, to maintain therapeutic drug concentrations. See prescribing information for tacrolimus.
Interactions with Investigations of Neuroendocrine Tumors	
Clinical Impact:	Serum chromogranin A (CgA) levels increase secondary to PPI-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors.
Intervention:	Discontinue NEXICURE 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.
Interaction with Secretin Stimulation Test	
Clinical Impact:	Hyper-response in gastrin secretion in response to secretin stimulation test, falselysuggesting gastrinoma.
Intervention:	Discontinue NEXICURE 4 weeks prior to testing.
False Positive Urine Tests for THC	
Clinical Impact:	There have been reports of false positive urine screening test for tetrahydrocannabinol(THC) in patients receiving PPIs.
Intervention:	An alternative confirmatory method should be considered to verify positive results.

Table 4: Clinically Relevant Interactions Affecting Esomeprazole When Co-Administered with OtherDrugs

CYP2C19 or CYP3A4 Inducers	
Clinical Impact:	Decreased exposure of esomeprazole when used concomitantly with strong inducers.
Intervention:	St. John's Wort, rifampin: Avoid concomitant use with Ritonavir-containing products: see prescribing information for specific drugs
Voriconazole	
Clinical Impact:	Increased exposure of esomeprazole.
Intervention:	Dose adjustment of NEXICURE is not normally required. However, in patients with Zollinger-Ellison syndrome, who may require higher doses, dosage adjustment may beconsidered. See prescribing information for voriconazole.

Central Administration for Pharmaceutical care Approval Date: 3/11 /2022 1st Revisor: Dr/Shaza
General Administration of Scientific Reference and Medical Inserts
Medical Inserts Administration According to: FDA

10 USE IN SPECIFIC POPULATIONS

10.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies with esomeprazole in pregnant women.

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 H_2-receptor antagonists or other controls.

Several studies have reported no apparent adverse short-term effects on the infant when single dose oral or intravenous omeprazole was administered to over 200 pregnant women as premedication for cesarean section under general anesthesia.

10.2 Lactation

Risk Summary

Esomeprazole is the S-isomer of omeprazole and limited data suggest that omeprazole may be present in human milk. There are no clinical data on the effects of esomeprazole on the breastfed infant or on milk production. The developmentaland health benefits of breastfeeding should be considered along with the mother's clinical need for NEXICURE and any potential adverse effects on the breastfed infant from NEXICURE or from the underlying maternal condition.

10.3 Pediatric Use

Healing of EE

Pediatric Patients 1 Year to 17 Years of Age

The safety and effectiveness of Esomeprazole for enteric coated granules for delayed release oral suspension have been established in pediatric patients 12 years to 17 years for short-term treatment (4 to 8 weeks) for healing of EE. The safety and effectiveness of Esomeprazole for enteric coated granules for delayed release oral suspension have been established in pediatric patients 1 year to 11 years for short-term treatment (up to 8 weeks) for healing of EE. Use of Esomeprazole for this indication is supported by evidence from adequate and well-controlled studies in adults with additional safety and pharmacokinetic data in pediatric patients 1 year to 17 years of age. The safety profile in pediatric patients 1 year to 17 years of age was similar to adults.

Pediatric Patients 1 Month to Less Than 1 Year of Age

The safety and effectiveness of Esomeprazole for enteric coated granules for delayed release oral suspension have been established in pediatric patients 1month to less than 1 year of age for short-term treatment (up to 6 weeks) of EE due to acid-mediated GERD. Use of Esomeprazole for this indication is supported by evidence from adequate and well-controlled studies in adults with additional safety, pharmacokinetic, and pharmacodynamic data in pediatric patients 1 month to less than 1 year of age. The safety profile in pediatric patients 1 month to less than 1 year of age was similar to adults.

The safety and effectiveness of Esomeprazole for the treatment of EE due to acid-mediated GERD in pediatric patients lessthan 1 month of age have not been established.

Symptomatic GERD

Pediatric Patients 1 Year to 17 Years of Age

The safety and effectiveness of Esomeprazole for enteric coated granules for delayed release oral suspension have been established in pediatric patients 12 years to 17 years of age for the short-term treatment (4 weeks) of heartburn and other symptoms associated with GERD. The safety and effectiveness of Esomeprazole for enteric coated granules for delayed release oral

Central Administration for Pharmaceutical care Approval Date: 3/11 /2022 1st Revisor: Dr/Shaza
General Administration of Scientific Reference and Medical Inserts
Medical Inserts Administration According to: FDA

suspension have been established in pediatric patients 1 year to 11 years of age for the short-term treatment (up to 8 weeks) of heartburn and other symptoms associated with GERD. Use of Esomeprazole for this indication is supported by evidence from adequate and well-controlled studies in adults with additional safety and pharmacokinetic data in pediatric patients 1 year to 17 years of age. The safety profile in pediatric patients 1 year to 17 years of age was similar to adults.

The safety and effectiveness of Esomeprazole for the treatment of symptomatic GERD in pediatric patients less than 1 year ofage have not been established.

Infants 1 Month to Less Than 1 Year of Age

Esomeprazole was not found to be effective in a multicenter, randomized, double-blind, controlled, treatment-withdrawal study of 98 infants aged 1 month to 11 months for the treatment of symptomatic GERD. Patients were enrolled if they hadeither a clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD. Twenty of 98 enrolled patients underwent endoscopy, and 6 patients were found to have EE on endoscopy at baseline. All patients received Esomeprazole for enteric coated granules for delayed release oral suspension once daily during a two-week, open-label phase of the study.

There were 80 patients who attained a pre-specified level of symptom improvement and who entered the double-blind phase, in which they were randomized in equal proportions to receive NEXICURE or placebo for the next four weeks. Efficacy was assessed by observing the time from randomization to study discontinuation due to symptom worsening during the four-week, treatment-withdrawal phase. There was no statistically significant difference between Esomeprazole andplacebo in the rate of discontinuation due to symptom worsening; therefore, these results do not support the use of Esomeprazole for the treatment of symptomatic GERD in infants 1 month to less than 1 year of age.

Other Conditions

The safety and effectiveness of Esomeprazole for the risk reduction of NSAID-associated gastric ulcer, *H. pylori* eradicationto reduce the risk of duodenal ulcer recurrence and treatment of pathological hypersecretory conditions have not been established in pediatric

patients.

10.4 Geriatric Use

Of the total number of patients who received Esomeprazole in clinical trials, 1459 were 65 to 74 years of age and 354 patientswere 75 years of age and older.

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 elderly and younger patients, but greatersensitivity of some older individuals cannot be ruled out.

10.5 Hepatic Impairment

In patients with severe hepatic impairment (Child-Pugh Class C) exposure to esomeprazole substantially increased compared to healthy subjects. Dosage modification of NEXICURE is recommended for patients with severe hepatic impairment for the healing of EE, risk reduction of NSAID-associated gastric ulcer, *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence, and pathological hypersecretory conditions including Zollinger-Ellison Syndrome.

In patients with mild to moderate liver impairment (Child-Pugh Classes A and B), no dosage adjustment is necessary.

11 OVERDOSAGE

Manifestations in patients exposed to omeprazole, the racemic mixture, at doses up to 2,400 mg (120 times the usual recommended clinical dose) include confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen at recommended dosages. See the full prescribinginformation for omeprazole for complete safety information. 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 overdosage, treatment

Central Administration for Pharmaceutical care Approval Date: 3/11 /2022 1st Revisor: Dr/Shaza
General Administration of Scientific Reference and Medical Inserts
Medical Inserts Administration According to: FDA

should be symptomatic and supportive.

If over-exposure occurs, call your Poison Control Center for current information on the management ofpoisoning or overdosage.

12 DESCRIPTION

Enteric Coated free flowing granules for delayed release oral suspension after reconstitution

NEXICURE is supplied in enteric coated granules for delayed release oral suspension.

The esomeprazole granules and inactive granules are constituted with water toform a suspension and are given by oral, nasogastric, or gastric administration.

13 CLINICAL PHARMACOLOGY

13.1 Mechanism of Action

Esomeprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that suppresses gastric acid secretion by specific inhibition of the H+/K+ ATPase enzyme system at the secretory surface of the gastric parietal cell. Esomeprazole is protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, theachiral sulphenamide. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, esomeprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus.

13.2 Pharmacodynamics

Antisecretory Activity

Adults

The effect of esomeprazole on intragastric pH was determined in adult patients with symptomatic GERD in two separate studies. In the first study of 36 patients, Esomeprazole 40 mg and 20 mg delayed-release capsules were administered once daily over 5 days as shown in Table 5:

Parameter	Esomeprazole Delayed-Release Capsules	
	40 mg once daily	20 mg once daily
% Time Gastric pH >4[1] (Hours)	70%[2] (16.8 h)	53% (12.7 h)
Coefficient of variation	26%	37%
Median 24 Hour pH	4.9[2]	4.1
Coefficient of variation	16%	27%

1. Gastric pH was measured over a 24-hour period
2. p<0.01 Esomeprazole 40 mg vs. Esomeprazole 20 mg

Pediatrics

In infants (1 to 11 months old, inclusive) with GERD given Esomeprazole for enteric coated granules for delayed release oral suspension 1 mg/kg oncedaily, the percent time with intragastric pH > 4 increased from 29% at baseline to 69% on Day 7, which is similar to thepharmacodynamic effect in adults.

Serum Gastrin Effects

The effect of esomeprazole on serum gastrin concentrations was evaluated in approximately 2,700 patients in clinical trials of oral esomeprazole for up to 8 weeks and in over 1,300 patients for up to 12 months. The mean fasting gastrinlevel increased in a dose-related manner. The increase in serum gastrin concentrations reached a plateau within two tothree months of therapy and returned to baseline levels within four weeks after discontinuation of therapy.

Increased gastrin causes enterochromaffin-like cell hyperplasia and increased serum Chromogranin A (CgA) levels. Theincreased CgA levels may cause false positive results in diagnostic investigations for neuroendocrine tumors

Central Administration for Pharmaceutical care Approval Date: 3/11 /2022 1st Revisor: Dr/Shaza
General Administration of Scientific Reference and Medical Inserts
Medical Inserts Administration According to: FDA

Enterochromaffin-like (ECL) Cell Effects

Human gastric biopsy specimens have been obtained from more than 3,000 patients (both pediatrics and adults) treated with omeprazole in long-term clinical trials. The incidence of ECL cell hyperplasia in these studies increased with time;however, no case of ECL cell carcinoids, dysplasia, or neoplasia has been found in these patients

In over 1,000 patients treated with oral esomeprazole (10 mg, 20 mg or 40 mg/day) for up to 12 months, the prevalence of ECL cell hyperplasia increased with time and dose. No patient developed ECL cell carcinoids, dysplasia, or neoplasia in the gastric mucosa.

Endocrine Effects

Oral doses of omeprazole 30 mg or 40 mg once daily for 2 to 4 weeks had no effect on carbohydrate metabolism,circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecystokinin, or secretin.

13.3 Pharmacokinetics

Absorption

Esomeprazole for enteric coated granules for delayed release oral suspension. Showed similar bioavailability aftera single dose (40 mg) administration in 94 healthy male and female subjects under fasting conditions. After oral administration, peak plasma levels (Cmax) of esomeprazole occur at approximately 1.5 hours (Tmax). The Cmax increases proportionally when the dose is increased, and there is a three-fold increase in the area under the plasma concentration- time curve (AUC) from 20 to 40 mg. At repeated once-daily dosing with 40 mg, the systemic bioavailability is approximately 90% compared to 64% after a single dose of 40 mg. The mean exposure (AUC) to esomeprazole increases from 4.32 micromol*hr/L on Day 1 to 11.2 micromol*hr/L on Day 5 after 40 mg once daily dosing.

Esomeprazole is a time-dependent inhibitor of CYP2C19, resulting in autoinhibition and nonlinear pharmacokinetics. Thesystemic exposure increases in a more than dose

proportional manner after multiple oral doses of esomeprazole.

Compared to the first dose, the systemic exposure (Cmax and AUC0-24h) at steady state following once a day dosing increased by 43% and 90%, respectively, compared to after the first dose for the 20 mg dose and increased by 95% and159%, respectively, for the 40 mg dose.

Distribution

Esomeprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 2 to 20micromol/L. The apparent volume of distribution at steady state in healthy subjects is approximately 16 L.

Elimination

Metabolism

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 CYP3A4 whichforms the sulphone metabolite.

Excretion

The plasma elimination half-life of esomeprazole is approximately 1 to 1.5 hours. Less than 1% of parent drug is excretedin the urine. Approximately 80% of an oral dose of esomeprazole is excreted as inactive metabolites in the urine, and the remainder is found as inactive metabolites in the feces.

Specific Populations

Geriatric Patients

The AUC and Cmax values of esomeprazole were slightly higher (25% and 18%, respectively) in the elderly as compared to younger subjects at steady state. This increase in exposure is not considered clinically relevant.

Central Administration for Pharmaceutical care Approval Date: 3/11 /2022 1st Revisor: Dr/Shaza
General Administration of Scientific Reference and Medical Inserts
Medical Inserts Administration According to: FDA

Pediatric Patients

1 Month to 11 Months of Age

The pharmacokinetic parameters following repeated dose administration of esomeprazole magnesium 1 mg/kg once dailyfor 7 to 8 days in 1 month to 11-month-old infants with GERD are summarized in Table 6.

Table 6: Summary of Esomeprazole Pharmacokinetic Parameters Following Once Daily Dosing of Oral Esomeprazole Magnesium for 7 to 8 Days in 1 Month to 1 Year Old Infants with GERD

Parameter	Esomeprazole Magnesium 1 mg/kgOrally Once Daily
AUC (micromol·h/L) (n=7)[1]	3.51
Css,max (micromol/L) (n=15)[1]	0.87
t½ (h) (n=8)[1]	0.93
tmax (h) (n=15)[2]	3.0

1. Geometric mean
2. Median

Subsequent pharmacokinetic simulation analyses showed that for pediatric patients 1 month to 11 months of age, a dosageregimen of 2.5 mg once daily (body weight 3 to 5 kg), 5 mg once daily (body weight more than 5 to 7.5 kg) and 10 mg once daily for (body weight more than 7.5 to 12 kg) would achieve comparable steady-state plasma exposures (AUC) to that observed with 10 mg once daily in patients 1 year to 11 year of age and 20 mg once daily in patients 12 years to 18 years of age, as well as adults.

Apparent clearance (CL/F) increases with age in pediatric patients with GERD from 1 month to 2 years of age.

1 Year to 11 Years of Age

The pharmacokinetics of esomeprazole were studied in pediatric patients with GERD aged 1 year to 11 years. Followingonce daily dosing with Esomeprazole for enteric coated granules for delayed release oral suspension for 5 days, the total exposure (AUC) for the 10 mgdosage in patients aged 6 years to 11 years was similar to that seen with the 20 mg dosage in adults and adolescents aged12 years to 17 years. The total exposure for the 10 mg dosage in patients aged 1 year to 5 years was approximately 30% higher than the 10 mg dosage in patients aged 6 years to 11 years. The total exposure for the 20 mg dosage in patients aged 6 years to 11 years was higher than that observed with the 20 mg dosage in patients aged 12 years to 17 years and adults, but lower than that observed with the 40 mg dosage in 12 to 17 year-olds and adults. See Table 7.

Table 7: Summary of Esomeprazole Pharmacokinetic Parameters Following Once Daily Dosing of Esomeprazole for Enteric Coated Granules for Delayed Release Oral Suspension for 5 Days in 1 Year to 11 Year Old Patients with GERD

Parameter	Esomeprazole For Coated Granules for Oral Suspension		
	1 Year to 5 Years	6 Years to 11 Years	
	10 mg once daily (N=8)	10 mg once daily (N=7)	20 mg once daily (N=6)
AUC (micromol·h/L)[1]	4.83	3.70	6.28
Cmax (micromol/L)[1]	2.98	1.77	3.73
tmax (h)[2]	1.44	1.79	1.75
t½λz (h)[1]	0.74	0.88	0.73
Cl/F (L/h)[1]	5.99	7.84	9.22

1 Geometric mean

2 Arithmetic mean

12 Years to 17 Years of Age

Central Administration for Pharmaceutical care Approval Date: 3/11 /2022 1st Revisor: Dr/Shaza
General Administration of Scientific Reference and Medical Inserts
Medical Inserts Administration According to: FDA

The pharmacokinetics of Esomeprazole were studied in 28 adolescent patients with GERD aged 12 to 17 years inclusive, in a single center study. Patients were randomized to receive Esomeprazole 20 mg or 40 mg once daily for 8 days. Mean C_{max} and AUC values of esomeprazole were not affected by body weight or age; and more than dose-proportional increases in mean C_{max} and AUC values were observed between the two dose groups in the study. Overall, Esomeprazole pharmacokinetics in adolescent patients aged 12 to 17 years were similar to those observed in adult patients with symptomatic GERD. See Table 8.

Table 8: Comparison of Esomeprazole Pharmacokinetic Parameters Following Once Daily Dosing of Esomeprazole Delayed-Release Capsules in Pediatric Patients 12 Years to 17 Years with GERD and Adults with Symptomatic GERD[1]

Parameter	Esomeprazole Delayed-Release Capsules			
	12 Years to 17 Years (N=28)		Adults (N=36)	
	20 mg once daily for 8 days	40 mg once daily for 8 days	20 mg once daily for 5 days	40 mg once daily for 5 days
AUC (micromol h/L)	3.65	13.86	4.2	12.6
C_{max} (micromol/L)	1.45	5.13	2.1	4.7
t_{max} (h)	2.00	1.75	1.6	1.6
t½λz (h)	0.82	1.22	1.2	1.5
Data presented are geometric means for AUC, C_{max} and t½λz, and median value for t_{max}				

1. Data obtained from two independent studies

Patients with Renal Impairment

The pharmacokinetics of Esomeprazole in patients with renal impairment are not expected to be altered relative to healthysubjects as less than 1% of esomeprazole is excreted unchanged in urine.

Drug Interaction Studies

Effect of Esomeprazole/Omeprazole on Other Drugs

In vitro and *in vivo* studies have shown that esomeprazole is not likely to inhibit CYPs 1A2, 2A6, 2C9, 2D6, 2E1 and3A4.

Antiretrovirals

For some antiretroviral drugs, such as rilpivirine, atazanavir and nelfinavir, decreased serum concentrations havebeen reported when given together with omeprazole.

-Rilpivirine:

Following multiple doses of rilpivirine (150 mg, daily) and omeprazole (20 mg, daily), AUC was decreased by 40%,Cmax by 40%, and Cmin by 33% for rilpivirine.

-Nelfinavir:

Following multiple doses of nelfinavir (1250 mg, twice daily) and omeprazole (40 mg daily), AUC was decreased by36% and 92%, Cmax by 37% and 89% and Cmin by 39% and 75% respectively for nelfinavir and M8.

-Atazanavir:

Following multiple doses of atazanavir (400 mg, daily) and omeprazole (40 mg, daily, 2 hours before atazanavir),AUC was decreased by 94%, Cmax by 96%, and Cmin by 95%.

-Saquinavir:

Following multiple dosing of saquinavir/ritonavir (1000/100 mg) twice daily for 15 days with omeprazole 40 mg daily co-administered days 11 to 15. The AUC was increased by 82%, Cmax by 75%, and Cmin by 106%. The mechanism behind this interaction is not fully elucidated.

Clopidogrel

In a crossover study, healthy subjects were administered clopidogrel (300 mg loading dose followed by 75 mg per day as the maintenance dosage for 28 days) alone and with

Central Administration for Pharmaceutical care Approval Date: 3/11 /2022 1st Revisor: Dr/Shaza
General Administration of Scientific Reference and Medical Inserts
Medical Inserts Administration According to: FDA

esomeprazole (40 mg orally once daily at the same time as clopidogrel) for 29 days. Exposure to the active metabolite of clopidogrel was reduced by 35% to 40% over this time period when clopidogrel and esomeprazole were administered together. Pharmacodynamic parameters were also measuredand demonstrated that the change in inhibition of platelet aggregation was related to the change in the exposure to clopidogrel active metabolite.

Mycophenolate Mofetil

Administration of omeprazole 20 mg twice daily for 4 days and a single 1000 mg dose of MMF approximately one hourafter the last dose of omeprazole to 12 healthy subjects in a cross-over study resulted in a 52% reduction in the Cmax and 23% reduction in the AUC of MPA.

Cilostazol

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 study, increased Cmax and AUC of cilostazol by 18% and 26% respectively. The Cmax and AUC ofone of the active metabolites, 3,4-dihydro-cilostazol, which has 4 to 7 times the activity of cilostazol, were increased by29% and 69%, respectively. Co-administration of cilostazol with omeprazole is expected to increase concentrations of cilostazol and the above mentioned active metabolite.

Diazepam

Co-administration of esomeprazole 30 mg and diazepam, a CYP2C19 substrate, resulted in a 45% decrease in clearance ofdiazepam. Increased plasma levels of diazepam were observed 12 hours after dosing and onwards. However, at that time, the plasma levels of diazepam were below the therapeutic interval, and thus this interaction is unlikely to be of clinical relevance.

Digoxin

Concomitant administration of omeprazole 20 mg once daily and digoxin in healthy subjects increased the bioavailabilityof digoxin by 10% (30% in two subjects).

Other Drugs

Concomitant administration of esomeprazole and either naproxen (non-selective NSAID) did not identify any clinicallyrelevant changes in the pharmacokinetic profiles of these NSAIDs.

Effect of Other Drugs on

Esomeprazole/Omeprazole

St. John's Wort

In a cross-over study in 12 healthy male subjects, St. John's Wort (300 mg three times daily for 14 days) significantly decreased the systemic exposure of omeprazole in CYP2C19 poor metabolizers (Cmax and AUC both decreased by 38%)and extensive metabolizers (Cmax and AUC decreased by 50% and 44%, respectively).

Voriconazole

Concomitant administration of omeprazole and voriconazole (a combined inhibitor of CYP2C19 and CYP3A4) resulted inmore than doubling of the omeprazole exposure. When voriconazole (400 mg every 12 hours for one day, followed by 200 mg once daily for 6 days) was given with omeprazole (40 mg once daily for 7 days) to healthy subjects, the steady- state Cmax and AUC0-24 of omeprazole significantly increased: an average of 2 times (90% CI: 1.8, 2.6) and 4 times (90% CI: 3.3, 4.4), respectively, as compared to when omeprazole was given without voriconazole.

Other Drugs

Co-administration of esomeprazole with oral contraceptives, diazepam, phenytoin, quinidine, naproxen (non-selectiveNSAID) did not seem to change the pharmacokinetic profile of esomeprazole.

13.4 Microbiology

Esomeprazole, amoxicillin, and clarithromycin triple therapy has been shown to be active against most strains of *Helicobacterpylori (H. pylori) in vitro* and in clinical infections.

Central Administration for Pharmaceutical care Approval Date: 3/11 /2022 1st Revisor: Dr/Shaza
General Administration of Scientific Reference and Medical Inserts
Medical Inserts Administration According to: FDA

Helicobacter pylori: Susceptibility testing of *H. pylori* isolates was performed for amoxicillin and clarithromycin usingagar dilution methodology, and minimum inhibitory concentrations (MICs) were determined.

Pretreatment Resistance: Clarithromycin pretreatment resistance rate (MIC ≥ 1 mcg/mL) to *H. pylori* was 15% (66/445) at baseline in all treatment groups combined. A total of > 99% (394/395) of patients had *H. pylori* isolates that were considered to be susceptible (MIC ≤ 0.25 mcg/mL) to amoxicillin at baseline. One patient had a baseline *H. pylori* isolatewith an amoxicillin MIC = 0.5 mcg/mL.

14 STORAGE

NEXICURE enteric coated granules for delayed release oral suspension is stored at temperature not exceeding 30 °C, in dry place.

15 SHELF LIFE:

24 Months

16 PACKAGE:

Nexicure 2.5, 5,10 and 20 Sachets:

Pack of 7, 10, 14 and 28 Free { (polyester /Al/ Low Density Polyethylene) From Outside to Inside } Sachets each Contains 3000 mg Granules

Manufactured by

Zeta Pharma for Pharmaceutical Industries (Zeta Pharma)

نيكسيكيور

إيزوميبرازول2.5، 5، 10 و 20 مجم

حبيبات معوية مغلفة للتعليق الفموي متأخرالانطلاق

ما هي أهم المعلومات التي يجب أن أعرفها عن نيكسيكيور؟

قد يساعد النيكسيكيور الأعراض المتعلقة بالحموضة، ولكن قد يبقي لديك بعض مشاكل المعدة الخطيرة. تحدث إلي طبيبك.

قد يتسبب النيكسيكيور في بعض الآثار الجانبية الخطيرة، والتي تتضمن:

- **نوع من أنواع مشاكل الكلي (التهاب الكلية الخلالي الحاد).** بعض الناس الذين يتناولون أدوية مثبط مضخة البروتون، بما فيهم النيكسيكيور، قد يتولد لديهم مشكلة بالكلي تسمي **التهاب الكلية الخلالي الحاد والذي قد يحدث في اي وقت أثناء العلاج بالنيكسيكيور. تحدث إلي طبيبك علي الفور في حالة انخفاض في كمية البول لديك او في حالة وجود دم بالبول.**
- **إسهال في الأمعاء لديك بسبب عدوي** (كلوستريديوديز ديفيسيل) تحدث إلي طبيبك علي الفور في حالة وجود براز مائي او الم بالمعدة والذي لا يزول. قد يكون أو لا يكون لديك حمي.
- **كسور بالعظم (الفخذين، المعصم، أو العمود الفقري).** قد تحدث الكسور بالعظم في الفخذين، المعصم، أو العمود الفقري لدي الناس الذين يتناولون جرعات يومية متعددة من أدوية مثبط مضخة البروتون لمدة طويلة من الوقت (سنه أو أكثر). اخبر طبيبك إذا كان لديك كسر في العظام خاصة في الفخذين، المعصم أو العمود الفقري.
- **بعض أنواع الذنبة الحمراء.** الذنبة الحمراء هي مرض مناعي ذاتي (تهاجم خلايا الجسم الخلايا الأخري أو الأعضاء في الجسم). بعض الأشخاص الذين يتناولون ادوية مثبط مضخة البروتون، بما فيهم النيكسيكيور، قد يتولد لديهم بعض انواع الذنبة الحمراء أو قد تسوء الذنبة إذا كان لديهم المرض بالفعل. تحدث إلي طبيبك علي الفور إذا كان لديك الم مفصل جديد او الألم لديك يتدهور أو كان لديك طفح جلدي علي الخد أو الأذرع والتي تزداد سوءاً في الشمس.

تحدث إلي طبيبك عن خطر غرضتك لهذه الآثار الجانبية

قد يكون للنيكسيكيور اثار جانبية خطيرة أخري. انظر " ما هي الآثار الجانبية المحتملة للنيكسيكيور؟"

ما هو النيكسيكيور؟

دواء بوصفة طبية يسمي مثبط المضخة البروتونية، يستخدم لتقليل نسبة الحمض بمعدتك.

يستخدم النيكسيكيور في الكبار لـ:

- من 4 إلي 8 أسابيع لشفاء وإزالة أعراض تلف المريء ذو الصلة بالحمض (التهاب المريء البوزيني أو التهاب المريء). قد يصف طبيبك من 4 إلي 8 أسابيع أخريين من النيكسيكيور للمرضي الذين لديهم التهاب مريء لا يشفي.

- المحافظة علي الشفاء من التهاب المريء
- 4 إلي 8 أسابيع لعلاج حرقة المعدة والأعراض الأخري التي تحدث مع مرض الجزر المعدي المريئي (إرتجاع المريء)
- مدة تصل إلي 6 أشهر لتقليل خطورة قرح المعدة لدي بعض الأشخاص الذين يتناولون أدوية الألم والتي تسمي مضادات الالتهاب غير الستيرويدية
- علاج مرضى التهابات المعدة (جرثومة المعدة) وقرحة المعدة، بالإضافة إلي المضادات الحيوية اموكسيسيلين وكلاريثروميسين.
- العلاج طويل الأمد للحالات التي تفرز فيها معدتك الكثير من الأحماض، بما في ذلك متلازمة زولينجر إليسون. متلازمة زولينجر إليسون هي حالة نادرة تنتج فيها المعدة كمية من الحمض أكثر من المعتاد.

يستخدم نيكسيكيور في الأطفال والمراهقين الذين تتراوح أعمارهم ما بين 12 لـ 17 سنة لـ

- 4 إلي 8 أسابيع للشفاء من التهاب المريء.
- 4 أسابيع لعلاج حرقة المعدة والأعراض الأخري التي تحدث مع ارتجاع المريء.

يستخدم نيكسيكيور في الأطفال من 1 إلي 11 سنة لـ

- 8 أسابيع للشفاء من التهاب المريء.
- مدة تصل إلي 8 أسابيع لعلاج حرقة المعدة والأعراض الأخري التي تحدث مع إرتجاع المريء.

يستخدم النيكسيكيور في الأطفال من شهر إلي أقل من سنة لعلاج إرتجاع المريء مع التهاب المريء لمدة تصل إلي 6 أسابيع.

من غير المعروف ما إذا كان النيكسيكيور امن وفعال للأطفال أقل من شهر لعلاج إرتجاع المريء مع التهاب المريء.

من غير المعروف ما إذا كان النيكسيكيور امن وفعال في للأطفال أقل من سنة لعلاج أعراض إرتجاع المريء.

من غير المعروف ما إذا كان النيكسيكيور آمن وفعال في للأطفال للحد من خطر الإصابة بقرح المعدة لدي الأطفال الذين يتناولون أدوية تسمي مضادات الالتهاب غير الستيرويدية، لعلاج عدوي جرثومة المعدة لتقليل خطر عودة قرحة المعدة، ولعلاج حالات حيث تنتج المعدة الكثير من الحمض.

لا تأخذ النيكسيكيور إذا كنت:

- لديك حساسية من المغنيسيوم إيسوميبرازول، أو أي أدوية من مثبط مضخة البروتون، أو أي من مكونات النيكسيكيور. راجع نهاية نليل النواء هذا للحصول علي قائمة كاملة بمكونات النيكسيكيور.

اخبر طبيبك علي الفور أو احصل علي مساعدة طبية طارئة إذا ظهرت عليك أي من الأعراض التالية لرد فعل تحسسي مع النيكسيكيور:

- o طفح جلدي
- o ضيق الحلق

Dr/Shaza 3/11/2022

تناول نيكسيكيور حبيبات معوية مغلفة للتعليق الفموي متأخر الانطلاق علي النحو التالي

- يأتي نيكسيكيور حبيبات معوية مغلفة للتعليق الفموي متأخر الانطلاق في أكياس فويل تحتوي علي تركيزات 2.5 مجم، 5 مجم، 10 مجم، أو 20 مجم.
- يجب عليك أن تستخدم سرنجة فموية لقياس كمية الماء المطلوب لخلط جرعتك. اطلب سرنجة فموية من الصيدلي الخاص بك.
- إذا كانت الجرعة الموصوفة لك هي 2.5 مجم أو 5 مجم، أضف 5 مل من الماء في وعاء، ثم أضف محتويات كيس الفويل الذي يحتوي علي الجرعة الموصوفة عن طريق طبيبك.
- **إذا كانت جرعتك الموصوفة هي 10 مجم أو 20 مجم ، أضف 15 مل من الماء إلى وعاء ، ثم أضف محتويات علبة رقائق تحتوي على الجرعة التي وصفها طبيبك .**
- إذا تم إرشادك أنت أو طفلك من قبل طبيبك باستخدام أكثر من فويل واحد للجرعة الموصوفة، اتبع تعليمات الخلط المزودة عن طريق الصيدلي أو الطبيب الخاص بك.
- قلب.
- اتركه من 2 إلي 3 دقائق ليصبح أكثر سمكاً.
- قلب وخذ الجرعة خلال 30 دقيقة. إذا لم يستخدم خلال 30 دقيقة، تخلص من هذه الجرعة وقم بخلط جرعة جديدة.
- إذا تبقي أي من الدواء بعد الشرب، أضف المزيد من الماء، قلب، وتناول الجرعة علي الفور.
- بالنسبة للأطفال الصغار ، يمكنك أن تعطي الدواء بالسرنجة الفموية. قم بغسل السرنجة الفموية بالماء بعد كل استخدام.

يمكنك إعطاء نيكسيكيور حبيبات معوية مغلفة للتعليق الفموي متأخر الانطلاق من خلال أنبوب أنفي معدي أو أنبوب معدي، كما موصي من قبل طبيبك.

ما هي الاثار الجانبية المحتملة للنيكسيكيور؟

يمكن أن يسبب نيكسيكيور آثارا جانبية خطيرة ، بما في ذلك:

• **راجع "ما أهم المعلومات التي يجب أن أعرفها عن نيكسيكيور؟"**

• يمكن أن يحدث انخفاض في مستويات فيتامين ب 12 في الجسم لدى الأشخاص الذين تناولوا نيكسيكيور لفترة طويلة (أكثر من 3 سنوات). أخبر طبيبك إذا كنت تعاني من أعراض انخفاض مستويات فيتامين ب 12 ، بما في ذلك ضيق التنفس، والدوار، وعدم انتظام ضربات القلب، وضعف العضلات، والجلد الشاحب، والشعور بالتعب، وتغيرات الحالة المزاجية، والوخز أو التنميل في الذراعين والساقين.

• **يمكن أن يحدث انخفاض في مستويات المغنيسيوم في الجسم** لدى الأشخاص الذين تناولوا نيكسيكيور لمدة 3 أشهر على

- انتفاخ في الوجه
- صعوبة في التنفس

تناول دواء يحتوي على ريلبيفيرين (أودیورانت، كومبليرا، أوديفسي) المستخدم لعلاج الإيدز (فيروس نقص المناعة البشرية).

قبل تناول النيكسيكيور ، أخبر طبيبك عن جميع حالاتك الطبية ، بما في ذلك إذا كنت:

- لديك انخفاض مستويات المغنيسيوم ، انخفاض مستويات الكالسيوم وانخفاض مستويات البوتاسيوم في الدم.
- لديك مشاكل في الكبد.
- حامل أو تخطط للحمل. من غير المعروف ما إذا كان النيكسيكيور سوف يؤذي طفلك المحتمل.
- ترضع رضاعة طبيعية أو تخطط للرضاعة. من الممكن أن ينتقل النيكسيكيور عبر لبن الثدي. تحدث إلي طبيبك عن أفضل طريقة لإرضاع طفلك إذا كنت تتناول النيكسيكيور.

أخبر طبيبك عن جميع الأدوية التي تتناولها ، بما في ذلك الأدوية التي تصرف دون وصفة طبية والفيتامينات والمكملات العشبية.

أخبر طبيبك بشكل خاص إذا كنت تتناول: كلوبيدوجريل (بلافيكس)، ميثوتريكسات (أوترزات، رامسوفو، تريكسال، زالميب)، ديجوكسين (لانوكسين)، ريلبيفيرين (أوديورانت)، نبتة سانت جون (هيبريكيم بيرفوراتم)، أو ريفامبين (ريماستان، ريفاتير، ريفاميت)

كيف يجب أن أتناول نيكسيكيور؟

• تناول نيكسيكيور تمامًا كما وصفه طبيبك.

• لا تغير جرعتك أو توقف نيكسيكيور دون التحدث مع طبيبك.

• تناول نيكسيكيور قبل الوجبة على الأقل بساعة واحدة.

• يمكن تناول مضادات الحموضة مع النيكسيكيور.

• لا تسحق أو تمضغ الحبيبات. تأكد من ابتلاع عصير التفاح على الفور. تخلص من أي خليط متبقي. لا تقم بتخزينه لاستخدامه لاحقًا

• إذا نسيت تناول جرعة من نيكسيكيور ، تناولها حالما تتذكرها. إذا حان الوقت تقريبًا للجرعة التالية ، فلا تتناول الجرعة الفائتة. تناول الجرعة التالية في الوقت المحدد. لا تتناول جرعة مضاعفة لتعويض الجرعة المنسية.

• إذا كنت تتناول الكثير من نيكسيكيور ، اتصل بطبيبك أو مركز مكافحة السموم المحلي على الفور ، أو اذهب إلى أقرب غرفة طوارئ في المستشفى.

معلومات عامة حول الاستخدام الآمن والفعال للنيكسيكيور.

توصف الأدوية أحيانًا لأغراض أخرى غير تلك المدرجة في دليل الأدوية. لا تستخدم نيكسيكيور للحالة التي لم يتم وصفه لها.

لا تعطي نيكسيكيور للأشخاص الاخرين، حتى و لو كان لديهم نفس الأعراض التي لديك. قد يضرهم.

يمكنك أن تطلب من الصيدلي أو الطبيب الحصول على معلومات حول نيكسيكيور والتي تكون مكتوبة للمهنيين الصحيين.

ما هي مكونات نيكسيكيور حبيبات معوية مغلفة للتعليق الفموي متأخر الانطلاق ؟

المواد الفعالة

نيكسيكيور 2.5 مجم: 29.413 مجم إيزوميبرازول مغنيسيوم ثلاثي هيدرات 8.5٪ MUPs ما يعادل 2.5 مجم إيزوميبرازول

نيكسيكيور 5 مجم: 58.83 مجم إيزوميبرازول مغنيسيوم ثلاثي هيدرات 8.5٪ MUPs ما يعادل 5 مجم إيزوميبرازول

- نيكسيكيور 10 مجم 117.65 مجم إيزوميبرازول مغنيسيوم ثلاثي هيدرات 8.5٪ MUPs ما يعادل 10 مجم إيزوميبرازول

- نيكسيكيور 20 مجم :235.3 مجم إيزوميبرازول مغنيسيوم ثلاثي هيدرات 8.5٪ MUPs ما يعادل 20 مجم إيزوميبرازول

المواد الغير فعالة

مالتوديكسترين، حامض الستريك اللامائي، سكر الوز ، كينولين أصفر (رقم CI: 47005)، صمغ الزانثان، نكهة الفراولة الجافة، ثاني أكسيد السيليكون الغرواني (إيروسيل 200)، بوفيدون K30، كحول الأيزوبروبيل

التبليغ عن الأعراض الجانبية

اذا كنت تعرضت لأي من تلك الآثار الجانبية، تحدث إلى طبيبك أو الصيدلي. وهذا يشمل أي آثار غير مدرجة في هذه النشرة. يمكنك أيضًا الإبلاغ لمركز اليقظة الدوائية المصري :

Email: pv.followup@edaegypt.gov.eg

زيتا فارما للصناعات الدوائية "زيتا فارما

E-mail: PV@zeta-pharma.com

محتويات العبوة ومعلومات أخرى

نيكسيكيور 2.5 مجم ، 5 مجم ، 10 مجم ، 20 مجم اكياس جرعة واحدة تحتوي على حبيبات ناعمة صفراء باهتة إلى أصفر تعطي معلق أصفر باهتًا إلى أصفر.

العبوة:

الأقل.

أخبر طبيبك على الفور إذا كنت تعاني من أعراض انخفاض مستويات المغنيسيوم ، بما في ذلك النوبات ، والدوخة ، وعدم انتظام ضربات القلب ، والعصبية ، والام العضلات أو ضعفها ، وتشنجات في اليدين أو القدمين أو الصوت

• **أورام المعدة (سلائل الغدة القاعدية).** الأشخاص الذين يتناولون ادوية مثبطات مضخة البروتون لفترة طويلة لديهم مخاطر متزايدة لتطوير نوع معين من نمو المعدة يسمى سلائل الغدة القاعدية ، خاصة بعد تناول أدوية مثبطات مضخة البروتون لأكثر من عام واحد.

• **تفاعلات جلدية شديدة** يمكن أن يسبب نيكسيكيور تفاعلات جلدية نادرة ولكنها شديدة قد تؤثر على أي جزء من جسمك. قد تحتاج هذه التفاعلات الجلدية الخطيرة إلى العلاج في المستشفى وقد تكون مهددة للحياة.

• طفح جلدي قد يكون مصحوبًا بتقرحات، تقشير أو نزيف في أي جزء من الجلد (بما في ذلك الشفاه، العينين، الفم، الأنف، الأعضاء التناسلية، اليدين أو القدمين).

• إذا سبق لك الإصابة برد فعل جلدي بعد العلاج بدواء مماثل لنيكسيكيور والذي يقلل من حمض المعدة. إذا ظهر لديك طفح جلدي، وخاصة في المناطق المعرضة لأشعة الشمس أخبر طبيبك بأسرع ما يمكن، فقد تحتاج إلى وقف العلاج بنيكسيكيور ، تذكر أيضاً ذكر أي آثار سلبية أخرى مثل الام المفاصل.

• قد تعاني أيضًا من الحمى، القشعريرة، الام الجسم، ضيق التنفس أو تضخم الغدد الليمفاوية.

توقف عن تناول نيكسيكيور واتصل بطبيبك على الفور. قد تكون هذه الأعراض هي العلامة الأولى لتفاعل جلدي شديد.

تشمل الآثار الجانبية الأكثر شيوعًا للنيكسيكيور ما يلي:

- صداع
- الام في المعدة (بطني)
- الإسهال
- الإمساك
- الغثيان
- جفاف الفم
- غاز

هذه ليست كل الآثار الجانبية المحتملة للنيكسيكيور.

استدعي الطبيب للحصول على المشورة الطبية حول الآثار الجانبية.

تقارير ما بعد التسويقية

الجهاز العضلي الهيكلي: كسور العظام

كيف يمكنني تخزين نيكسيكيور ؟

• قم بتخزين نيكسيكيور في درجة حرارة لا تتجاوز 30 °C في مكان جاف.

• حافظ على حاوية نيكسيكيور مغلقة بإحكام.

احفظ نيكسيكيور وجميع الأدوية بعيدًا عن متناول الأطفال.

الصلاحية : عامان

علبة كرتون تحتوي علي 7، 10، 14، 28 كيس (بوليستر / الومنيوم / بولي إيثيلين منخفض الكثافة) من الخارج إلى الداخل - يحتوي كل كيس على 3000 مجم حبيبات

المصنع و صاحب الرخصة:
زيتا فارما للصناعات الدوائية "زيتا فارما "