Approval Date: MM/DD/YYYY
Modification Date: MM/DD/YYYY

Package Insert for
HERNERA®
Neratinib Maleate
Film-Coated Tablet 40 mg

Please read the instructions carefully and use under the guidance of a physician

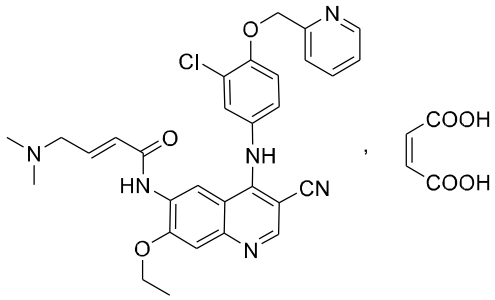
Dosage Form
Film-Coated Tablet

Characteristics
Red, oval, film-coated tablets which are white to pale yellow after removal of coating.

Composition
Each film-coated tablet contains neratinib maleate equivalent to neratinib 40 mg

Chemical name: (E)-*N*-{4-[3-chloro-4-(pyridine-2-ylmethoxy)anilino]-3-cyano-7-ethoxyquinolin-6-yl}-4-(dimethylamino)but-2-enamide maleate

Structure formula:



Molecular formula: $C_{30}H_{29}ClN_6O_3 \cdot C_4H_4O_4$
Molecular weight: 673.11 Daltons
Excipients: mannitol, copovidone, crospovidone, silicon dioxide, microcrystalline cellulose, magnesium stearate, film coating premix (gastric-soluble)

Indications

As a single agent for the extended adjuvant treatment of adult patients with early-stage (HER2)-positive breast cancer, to follow adjuvant trastuzumab based therapy.

In combination with capecitabine for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting.

Dosage and Administration

Premedication for Diarrhea

Antidiarrheal prophylaxis is recommended during the first 2 cycles (56 days) of treatment and should be initiated with the first dose of **Hernera** (*see [Dosage and Administration*] *Dose Escalation and [Warnings and Precautions]*).

Instruct patients to take loperamide as directed in Table 1, titrating to 1-2 bowel movements per day.

Table 1: Loperamide Prophylaxis

Time on **Hernera**	Loperamide Dose and Frequency
Weeks 1–2 (days 1–14)	4 mg three times daily
Weeks 3–4 (days 15–28)	4 mg twice daily
Weeks 5–8 (days 29–56)	4 mg twice daily
Weeks 9–52 (days 57-365)	4 mg as needed, not to exceed 16 mg per day

Hernera dose interruptions and dose reductions may also be required to manage diarrhea as clinically indicated (*see [Dosage and Administration] Dose Escalation*).

Recommended Dose and Schedule

Extended Adjuvant Treatment of Early-Stage Breast Cancer

The recommended dose of **Hernera** is 240 mg (six tablets) given orally once daily, with food, continuously until disease recurrence or for up to one year.

Advanced or Metastatic Breast Cancer

The recommended dose of **Hernera** is 240 mg (six tablets) given orally once daily with food on Days 1–21 of a 21-day cycle plus capecitabine (750 mg/m^2 given orally twice daily) on Days 1–14 of a 21-day cycle until disease progression or unacceptable toxicities.

Dose Escalation

A two week dose escalation for **Hernera** may be considered instead of starting at the 240 mg daily dose for patients with early-stage breast cancer and metastatic breast cancer, as described in Table 2 *[see Warnings and Precautions and Adverse Reactions]*.

Table 2: Hernera Dose Escalation and Treatment Schedule

Time on Hernera	Hernera Dose
Week 1 (days 1–7)	120 mg daily (three 40 mg tablets)
Week 2 (days 8–14)	160 mg daily (four 40 mg tablets)
Week 3 and onwards	240 mg daily (six 40 mg tablets, recommended dose)

If diarrhea occurs, treat with antidiarrheal medications, fluids, and electrolytes as clinically indicated. **Hernera** dose interruptions and dose reductions may also be required to manage diarrhea *[see Dosage and Administration]*.

Instruct patients to take **Hernera** at approximately the same time every day. **Hernera** tablets should be swallowed whole (tablets should not be chewed, crushed, or split prior to swallowing).

If a patient misses a dose, do not replace missed dose, and instruct the patient to resume **Hernera** with the next scheduled daily dose.

Dosage Modifications

Dosage Modifications for Adverse Reactions

Hernera dose modification is recommended based on individual safety and tolerability. Management of some adverse reactions may require dose interruption and/or dose reduction as shown in Table 3 to Table 6.
Discontinue **Hernera** for patients with adverse reactions that fail to recover to Grade 0–1 or baseline, with toxicities that result in a treatment delay >3 weeks, or if unable to tolerate 120 mg daily. Additional clinical situations may result in dose adjustments as clinically indicated (e.g. intolerable toxicities, persistent Grade 2 adverse reactions, etc.).

When **Hernera** is used in combination with capecitabine, refer to the capecitabine prescribing information for dose modifications of capecitabine.

Table 3: Hernera Monotherapy Dose Modifications for Adverse Reactions

Dose Level	Hernera Dose
Recommended starting dose	240 mg daily
First dose reduction	200 mg daily
Second dose reduction	160 mg daily
Third dose reduction	120 mg daily

Table 4: Hernera Monotherapy Dose Modifications and Management - General Toxicity[1]

Severity[2]	**Action**
Grade 3	Hold **Hernera** until recovery to ≤Grade 1 or baseline within 3 weeks. Then resume **Hernera** at the next lower dose level
Grade 4	Discontinue **Hernera** permanently

1 Refer to Table 5 and Table 6 below for manage diarrhea and hepatotoxicity
2 Per CTCAE v4.0

Dose Modifications for Diarrhea

Diarrhea management requires the correct use of antidiarrheal medication, diet modifications and recommended dosage modifications of **Hernera**. Guidelines for adjusting the dosage of **Hernera** in the event of liver toxicity are shown in Table 5.

Table 5: Dosage Modifications for Diarrhea

Severity[1]	**Action**
Grade 1 diarrhea [increase of <4 stools per day over baseline] Grade 2 diarrhea [increase of 4–6 stools per day over baseline] lasting ≤5 days Grade 3 diarrhea [increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; limiting self-care activities of daily living] lasting ≤2 days	Adjust antidiarrheal treatment Diet modifications Fluid intake of ~2L should be maintained to avoid dehydration Once event resolves to ≤ Grade 1or baseline, start loperamide 4 mg with each subsequent **Hernera** administration.
Any grade with complicated features[2] Grade 2 diarrhea lasting five days or longer[3] Grade 3 diarrhea lasting longer than 2 days[3]	Interrupt **Hernera** treatment Diet modifications Fluid intake of ~2L should be maintained to avoid dehydration If diarrhea resolves to Grade 0-1 in one week or less, then resume **Hernera** treatment at the same dose. If diarrhea resolves to Grade 0-1 in longer than one week, then resume **Hernera** treatment at reduced dose (see Tabel 3） Once event resolves to ≤ Grade 1 or baseline, start loperamide 4 mg with each subsequent **Hernera** administration.

Severity[1]	**Action**
Grade 4 diarrhea [Life-threatening consequences; urgent intervention indicated]	Permanently discontinue **Hernera** treatment
Diarrhea recurs to Grade 2 or higher at 120 mg per day	Permanently discontinue **Hernera** treatment

1 Per CTCAE v4.0
2 Complicated features include dehydration, fever, hypotension, renal failure, or Grade 3 or 4 neutropenia
3 Despite being treated with optimal medical therapy

Dose Modifications for Hepatotoxicity

Guidelines for dose adjustment of **Hernera** in the event of liver toxicity are shown in Table 6. Patients who experience ≥ Grade 3 diarrhea or any signs or symptoms of hepatotoxicity, such as worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia, should be evaluated for changes in liver function tests. Fractionated bilirubin and prothrombin time should also be collected during hepatotoxicity evaluation *[see Warnings and Precautions]*.

Table 6: Dose Modifications for Hepatotoxicity

Severity of Hepatoxicity[1]	**Action**
Grade 3 ALT（>5-20×ULN[2])or Grade 3 bilirubin（>3-10×ULN)	Hold **Hernera** until recovery to ≤ Grade 1 Evaluate alternative causes Resume **Hernera** at the next lower dose level if recovery to ≤ Grade 1 occurs within 3 weeks. If Grade 3 ALT or bilirubin occurs again despite one dose reduction, permanently discontinue **Hernera**
Grade 4 ALT（>20×ULN) or Grade 4 bilirubin（>10×ULN)	Permanently discontinue **Hernera** Evaluate alternative causes

1 Per CTCAE v4.0
2 ALT=Alanine Aminotransferase; ULN=Upper Limit Normal

Table 7: Hernera in Combination with Capecitabine Dose Modifications for Adverse Reactions

Dose Level	**Hernera Dose**
Recommended starting dose	240 mg daily (six 40 mg tablets)
First dose reduction	160 mg daily (four 40 mg tablets)
Second dose reduction	120 mg daily (three 40 mg tablets)

Table 8: Recommended Dosage Modifications for Adverse Reactions with Hernera in Combination with Capecitabine

Adverse Reaction	**Severity**†	**Action/Dose Modification**
Diarrhea *[see Warnings and Precautions]*	• Grade 1 Diarrhea [Increase of <4 stools per day over baseline] • Grade 2 Diarrhea [Increase of 4–6 stools per day over baseline] lasting ≤5 days • Grade 3 Diarrhea: [Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; limiting self- care and activities of daily living] lasting ≤2 days	• Adjust antidiarrheal treatment • Continue **Hernera** and capecitabine at full doses • Diet modifications • Fluid intake of ~2 L/day should be maintained to avoid dehydration • Once the event resolves to Grade ≤1 or baseline, start loperamide 4 mg with each subsequent **Hernera** administration

	• Persisting and intolerable Grade 2 Diarrhea: lasting >5 days • Grade 3 Diarrhea lasting >2 days • Grade 4 Diarrhea [Life-threatening consequences; urgent intervention indicated]	• Adjust antidiarrheal treatment • Hold **Hernera** and capecitabine until recovery to Grade ≤1 or baseline • Diet modifications • Fluid intake of ~2 L/day should be maintained intravenously, if needed • If recovery occurs: ≤1 week after withholding treatment, resume same doses of **Hernera** and capecitabine • Within 1–3 weeks after withholding treatment, reduce **Hernera** dose to 160 mg and maintain the same dose of capecitabine • If event occurs a second time and the **Hernera** dose has not already been decreased, reduce **Hernera** dose to 160 mg (maintain the same dose of capecitabine). If **Hernera** dose has already been reduced, then reduce the dose of capecitabine to 550 mg/m^2 given twice daily [a] (maintain the same dose of **Hernera**). • If subsequent events occur, reduce the dose of **Hernera** or capecitabine to the next lower dose level in an alternate fashion (i.e., reduce capecitabine to 375 mg/m^2 given twice daily [a] if **Hernera** was previously reduced, or reduce **Hernera** to 120 mg if capecitabine was previously reduced) • Once the event resolves to Grade ≤1 or baseline, start loperamide 4 mg with each subsequent **Hernera** administration

Hepatotoxicity *[see Warnings and Precautions]*	• Grade 3 ALT or AST (>5–20× ULN) OR • Grade 3 bilirubin (>3–10× ULN)	• Hold **Hernera** until recovery to ≤Grade 1 • Evaluate alternative causes • Resume **Hernera** at the next lower dose level if recovery to ≤Grade 1 occurs within 3 weeks. If Grade 3 ALT or AST, or bilirubin occurs again despite one dose reduction, permanently discontinue **Hernera**.
	• Grade 4 ALT or AST (>20× ULN) OR • Grade 4 bilirubin (>10× ULN)	• Permanently discontinue **Hernera** • Evaluate alternative causes
Other *[see Adverse Reactions]*	• Grade 3	• Hold **Hernera** until recovery to Grade ≤1 or baseline within 3 weeks of stopping treatment. Then resume **Hernera** at the next lower dose level.
	• Grade 4	• Discontinue **Hernera** permanently

ALT=Alanine Aminotransferase; AST=Aspartate Aminotransferase; ULN=Upper Limit Normal
† Per CTCAE v4.0
[a] Since capecitabine is provided as 150 mg or 500 mg tablets, it is recommended that the capecitabine dose reduction(s) is(are) rounded down to the nearest 500 mg or multiple of 150 mg for the twice daily dose. If the patient's body surface area is >2.0, the standard of care for the study center can be utilized for capecitabine mg/m^2 dosing.

Dose Modifications for Hepatic Impairment

No dose modifications are recommended for patients with mild to moderate hepatic impairment (Child Pugh A or B) *[see Adverse Reactions and Clinical Pharmacology]*.

Concomitant Use with Gastric Acid Reducing Agents

Proton pump inhibitors (PPI): Avoid concomitant use with **Hernera** [*see Drug Interactions*].

H_2-receptor antagonists: Take **Hernera** at least 2 hours before the next dose of the H2-receptor antagonist or 10 hours after the H_2-receptor antagonist [*see Drug Interactions*].
Antacids: Separate dosing of **Hernera** by 3 hours after antacids [*see Drug Interactions*].

Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed
- Co-administration with the following medical products that are strong inducers of the CYP3A4/P-gp isoform of cytochrome P450, such as:
  - Carbamazepine, phenytoin (antiepileptics)
  - St John's wort (Hypericum perforatum) (herbal product)
  - Rifampicin (antimycobacterial)
- Severe hepatic impairment (Child-Pugh C)

Warnings and Precautions

Diarrhea

Severe diarrhea and sequelae, such as dehydration, hypotension, and renal failure, have been reported during treatment with neratinib. Diarrhea was reported in 95% of neratinib-treated patients in ExteNET, a trial were not required to receive antidiarrheal prophylaxis. In the neratinib arm, Grade 3 diarrhea occurred in 40% and Grade 4 diarrhea occurred in 0.1% of patients. The majority of patients (93%) had diarrhea in the first month of treatment, the median time to first onset of Grade ≥ 3 diarrhea was 8 days (range, 1-350), and the median cumulative duration of Grade ≥ 3 diarrhea was 5 days (range, 1-139) *[see Adverse Reactions]*.

Diarrhea was reported in 83% of neratinib plus capecitabine treated patients in NALA, a randomized placebo-controlled trial in the metastatic breast cancer setting who were required to receive anti-diarrheal prophylaxis in the first 21-day cycle. The majority of patients (70%) had diarrhea in the first 21-day of treatment, the median time to first onset of Grade ≥3 diarrhea was 11 days (range, 2–728) and the median cumulative duration of Grade ≥3 diarrhea was 3 days (range, 1–21). In the neratinib plus capecitabine arm, Grade 3 diarrhea occurred in 24% of patients *[see Adverse Reactions]*.

Antidiarrheal prophylaxis has been shown to lower the incidence and severity of diarrhea. Instruct patients to initiate antidiarrheal prophylaxis with loperamide along with the first dose of **Hernera** and continue during the first two cycles (56 days) of treatment; after day 56, titrate dose to achieve 1–2 bowel movements per day and not to exceed 16 mg loperamide per day *[see Dosage and Administration]*. Consider adding other agents to loperamide as clinically indicated *[see Adverse Reactions]*.

Alternatively, a 2 weeks **Hernera** dose escalation approach prior to initiation of the recommended treatment regimen with **Hernera** can also be considered for diarrhea management *[see Dosage and Administration]*. For patients who used **Hernera** dose escalation, the median time to first onset of Grade ≥3 diarrhea was 45 days (range, 15–132) and the median cumulative duration of Grade ≥3 diarrhea was 2.5 days (range, 1– 6). Grade 3 diarrhea occurred in 13% of patients who used **Hernera** dose escalation *[see Adverse Reactions]*.

Monitor patients for diarrhea and treat with additional antidiarrheals as needed. When severe diarrhea with dehydration occurs, administer fluid and electrolytes as needed, interrupt

Hernera, and reduce subsequent doses *[see Dosage and Administration]*. Perform stool cultures as clinically indicated to exclude infectious causes of Grade 3 or 4 diarrhea or diarrhea of any grade with complicating features (dehydration, fever, neutropenia).

Hepatotoxicity

Hernera has been associated with hepatotoxicity characterized by increased liver enzymes. In ExteNET, 9.7% of patients experienced an alanine aminotransferase (ALT) increase ≥ 2 x ULN, 5.1% of patients experienced an aspartate aminotransferase (AST) increase ≥ 2 x ULN, and 1.7%of patients experienced an AST or ALT elevation > 5 x ULN (≥ Grade 3). Hepatotoxicity or increases in liver transaminases led to drug discontinuation in 1.7% of neratinib-treated patients.

In the NALA study, in neratinib and capecitabine-treated patients, 7% experienced an ALT or AST >3× ULN, 2% experienced ALT or AST >5× ULN, 7% experienced a bilirubin >1.5× ULN, and 1.3% experienced a bilirubin >3× ULN. Hepatotoxicity or increases in liver transaminases led to drug discontinuation in 0.3% of neratinib and capecitabine-treated patients.

Total bilirubin, AST, ALT, and alkaline phosphatase should be measured prior to starting treatment with **Hernera** monthly for the first 3 months of treatment, then every 3 months while on treatment and as clinically indicated. These tests should also be performed in patients experiencing Grade 3 diarrhea or any signs or symptoms of hepatotoxicity, such as worsening of fatigue, nausea, vomiting, right upper quadrant tenderness, fever, rash, or eosinophilia *[see Dosage Modifications in Dosage and Administration and Adverse Reactions]*.

Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, neratinib can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of neratinib to pregnant rabbits during organogenesis caused abortions, embryo-fetal death and fetal abnormalities in rabbits at maternal AUCs approximately 0.2 times the AUC in patients receiving the recommended dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for at least 1 month after the last dose. Advise male patients with femal partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of neratinib *[see Use in Pregnancy and Lactation, Clinical Pharmacology*].

Hepatic Impairment

No dosage modifications are recommended for patients with mild to moderate hepatic impairment (Child Pugh A or B). neratinib clearance is reduced, and C_{max} and AUC increase inpatients with severe, pre-existing hepatic impairment (Child Pugh C) *[see Dosage and Administration and Clinical Pharmacology]*.

Elderly
Elderly patients (≥65 years of age) are at a higher risk of renal insufficiency and dehydration which may be a complication of diarrhea and these patients should be carefully monitored.

Patients with a significant chronic gastrointestinal disorder
Patients with a significant chronic gastrointestinal disorder with diarrhea as a major symptom were not included in the pivotal study, and should be carefully monitored.

Renal impairment
Patients with renal impairment are at a higher risk of complications of dehydration if they develop diarrhoea, and these patients should be carefully monitored.

Left ventricular function
Left ventricular dysfunction has been associated with HER2 inhibition. neratinib has not been studied in patients with less than lower limit of normal left ventricular ejection fraction (LVEF) or with significant cardiac history. In patients with known cardiac risk factors, conduct cardiac monitoring, including assessment of LVEF, as clinically indicated.

Skin and subcutaneous tissue disorders
Neratinib is associated with skin and subcutaneous tissue disorders. Patients with symptomatic skin and subcutaneous tissue disorders should be carefully monitored.

Grapefruit and pomegranate
Grapefruit or pomegranate juice may inhibit CYP3A4 and/or P-gp and should be avoided during treatment with neratinib.

Drug Interactions
Effect of Other Drugs on **Hernera**

Table 9 includes drug interactions that affect the pharmacokinetics of **Hernera**.

Table 9: Drug Interactions That Affect Hernera

Gastric Acid Reducing Agents		
Clinical Impact	Concomitant use of **Hernera** with a proton pump inhibitor (PPI, lansoprazole) decreased Hernera C_{max} by 71% and AUC by 65% [*see Clinical Pharmacology*], H_2-receptor antagonist, or antacid may decrease neratinib AUC, which may reduce **Hernera** activity.	
Prevention or Management	PPIs	Avoid concomitant use of PPIs [*see Dosage and Administration*].
	H_2-receptor	Separate administration of **Hernera** at least 2 hours before or 10 hours after the H2-receptor antagonist dose [*see Dosage and Administration*].
	Antacids	Separate administration of **Hernera** by at least 3 hours after antacids [*see Dosage and Administration*].
Strong CYP3A4 Inhibitors		
Clinical Impact	Concomitant use of **Hernera** with a strong CYP3A4 inhibitor (ketoconazole) increased neratinib Cmax by 321% and AUC by 481% [*see Clinical Pharmacology*]. Concomitant use of **Hernera** with other strong or moderate CYP3A4 inhibitors may increase neratinib concentrations. Increased Neratinib concentrations may increase the risk of toxicity.	
Prevention or Management	Avoid concomitant use of **Hernera** with strong or moderate CYP3A4 inhibitors.	
Examples[1]	*Strong CYP3A4 inhibitors*: boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir and ritonavir, diltiazem, elvitegravir and ritonavir, grapefruit juice, idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, tipranavir and ritonavir, troleandomycin, voriconazole	
	Moderate CYP3A4 inhibitors: aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil	
Strong or Moderate CYP3A4 Inducers		

Clinical Impact	Concomitant use of **Hernera** with a strong CYP3A4 inducer (rifampin) reduced neratinib C_{max} by 76% and AUC by 87% *[see Clinical Pharmacokinetics]*. Concomitant use of **Hernera** with other strong or moderate CYP3A4 inducers may decrease **Hernera** concentrations. Decreased **Hernera** AUC may reduce **Hernera** activity.
Prevention or Management	Avoid concomitant use of **Hernera** with strong or moderate CYP3A4 inducers.
Examples[1]	*Strong CYP3A4 inducers*: carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort *Moderate CYP3A4 inducers*: bosentan, efavirenz, etravirine, modafinil

AUC=Area Under Curve; C_{max}=Maximum Concentration

1 These examples are a guide and not considered a comprehensive list of all possible drugs that may fit this category.

Effect of Hernera on Other Drugs

Certain P-glycoprotein (P-gp) Substrates

Concomitant use of **Hernera** with digoxin, a P-gp substrate, increased digoxin concentrations *[see Clinical Pharmacology]*. Increased concentrations of digoxin may lead to increased risk of adverse reactions including cardiac toxicity. Refer to the digoxin prescribing information for dosage adjustment recommendations due to drug interactions. **Hernera** may inhibit the transport of other P-gp substrates (e.g., dabigatran, fexofenadine).

Use in Pregnancy and Lactation

Contraception

Advise females of reproductive potential should undergo a pregnancy test before starting treatment with **Hernera** and to use effective contraception during treatment with **Hernera** and for at least 1 month after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of **Hernera**.

Pregnancy

Based on findings from animal studies and its mechanism of action, **Hernera** can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk of major birth defects is 5.6% and of miscarriage is 9.8% of clinically recognized pregnancies in the China general population.

Lactation

No data are available regarding the presence of neratinib or its metabolites in human milk or its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in breastfed infants from **Hernera**, advise lactating women not to breastfeed while taking **Hernera** and for at least 1 month after the last dose.

Pediatric Use

The safety and efficacy of **Hernera** in pediatric patients has not been established.

Geriatric Use

In the ExteNET trial, the average age is 52 years in the neratinib arm; 1236 patients were <65years, 172 patients were ≥65 years, of whom 25 patients were 75 years or older.

There was a higher frequency of treatment discontinuations due to adverse reactions in the ≥65 years age group than in the <65 years age group; in the neratinib arm, the percentages were 44.8% compared with 25.2%, respectively, and the incidence of serious adverse reactions were 9.9% and 7.0% respectively. The serious adverse reactions most frequently reported in the ≥ 65years-old group were vomiting (2.3%), diarrhea (1.7%), renal failure (1.7%), and dehydration (1.2%).

In the NALA trial, in the neratinib plus capecitabine arm; 242 patients were <65 years, 61 patients were ≥65 years, of whom 12 patients were 75 years or older. The incidence of serious adverse reactions in the neratinib plus capecitabine arm in the ≥65 years age group was 36% and in the <65 years age group was 34%. The serious adverse reactions most frequently reported in the ≥65 years-old group were diarrhea (16%), acute kidney injury (8%), and dehydration (7%). No overall differences in effectiveness were observed between patients ≥65 years old and patients <65 years old.

Adverse Reactions

Clinical Trials Experience

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.

Extended Adjuvant Treatment of Early-Stage Breast Cancer

ExteNET

The data described below reflect exposure of neratinib as a single agent in ExteNET, a multicenter, randomized, double-blind, placebo-controlled study of neratinib within 2 years after completion of adjuvant treatment with trastuzumab-based therapy in women with HER2- positive early-stage breast cancer. Patients who received neratinib in this trial were not required to receive any prophylaxis with antidiarrheal agents to prevent the neratinib-related diarrhea.

The median age was 52 years (60% were ≥ 50 years old, 12% were ≥ 65 years old); 81% were Caucasian, 3% Black or African American, 14% Asian and 3% other. A total of 1408 patients were treated with neratinib**.**

neratinib dose reduction due to an adverse reaction of any grade occurred in 31.2% of patients receiving neratinib compared to 2.6% of patients receiving placebo. Permanent discontinuation due to any adverse reaction was reported in 27.6% of neratinib-treated patients. The most common adverse reaction leading to discontinuation was diarrhea, accounting for 16.8% of neratinib-treated patients. The most common adverse reactions (>5%) were diarrhea, nausea, abdominal pain, fatigue, vomiting, rash, stomatitis, decreased appetite, muscle spasms, dyspepsia, AST or ALT increase, nail disorder, dry skin, abdominal distention, weight decreased and urinary tract infection. The most frequently reported Grade 3 or 4 adverse reactions were diarrhea, vomiting, nausea, and abdominal pain. Serious adverse reactions in the neratinib arm included diarrhea (1.6%), vomiting (0.9%), dehydration (0.6%), cellulitis (0.4%), renal failure (0.4%), erysipelas (0.4%), alanine aminotransferase increased (0.3%), aspartate aminotransferase increased (0.3%), nausea (0.3%), fatigue (0.2%), and abdominal pain (0.2%).

Table 10 summarizes the adverse reactions in ExteNET.

Table 10: Adverse Reactions Reported in ≥2% of Neratinib-Treated Patients in ExteNET

System Organ Class (Preferred Term)	Neratinib n=1408			Placebo n=1408		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Gastrointestinal Disorders						
Diarrhea	95	40	0.1	35	2	0
Nausea	43	2	0	22	0.1	0
Abdominal pain[1]	36	2	0	15	0.4	0
Vomiting	26	3	0	8	0.4	0
Stomatitis[2]	14	0.6	0	6	0.1	0
Dyspepsia	10	0.4	0	4	0	0
Abdominal distension	5	0.3	0	3	0	0
Dry mouth	3	0.1	0	2	0	0
General Disorders and Administration Site Conditions						
Fatigue	27	2	0	20	0.4	0
Hepatobiliary Disorders						
Alanine aminotransferase increased	9	1	0.2	3	0.2	0
Aspartate aminotransferase increased	7	0	0.2	3	0.3	0

Infections and Infestations						
Urinary tract infection	5	0.1	0	2	0	0
Investigations						
Weight decreased	5	0.1	0	0.5	0	0
Metabolism and Nutrition Disorders						
Decreased appetite	12	0.2	0	3	0	0
Dehydration	4	0.9	0.1	0.4	0.1	0
Musculoskeletal and Connective Tissue Disorders						
Muscle spasms	11	0.1	0	3	0.1	0
Respiratory, Thoracic and Mediastinal Disorders						
Epistaxis	5	0	0	1	0.1	0
Skin and Subcutaneous Tissue Disorders						
Rash[3]	18	0.6	0	9	0	0
Dry skin	6	0	0	2	0	0
Nail Disorder[4]	8	0.3	0	2	0	0
Skin fissures	2	0.1	0	0.1	0	0

1 Includes abdominal pain, abdominal pain upper, and abdominal pain lower
2 Includes stomatitis, aphthous stomatitis, mouth ulceration, oral mucosal blistering, mucosal inflammation, oropharyngeal pain, oral pain, glossodynia, glossitis, and cheilitis
3 Includes rash, rash erythematous, rash follicular, rash generalized, rash pruritic, rash pustular,rash maculo-papular, rash papular, dermatitis, dermatitis acneiform, and toxic skin eruption
4 Includes nail disorder, paronychia, onychoclasis, nail discoloration, nail toxicity, nail growth abnormal, and nail dystrophy

Advanced or Metastatic Breast Cancer

NALA

The data described below reflect the safety data of neratinib plus capecitabine in NALA, a randomized, multicenter, multinational, open-label, active-controlled study of HER2+ metastatic breast cancer in patients, with or without brain metastases, who have received two or more prior anti HER2-based regimens in the metastatic setting.

Patients were treated with neratinib 240 mg orally once daily Days 1–21 of a 21-day cycle in combination with capecitabine (750 mg/m^2 given orally twice daily) Days 1–14 of a 21-day cycle, or lapatinib 1250 mg orally once daily Days 1–21 of a 21-day cycle in combination with capecitabine (1000 mg/m^2 given orally twice daily) Days 1–14 of a 21-day cycle until disease progression. The median duration of treatment was 5.7 months in the neratinib plus capecitabine arm and 4.4 months in the lapatinib plus capecitabine arm.

neratinib dose reduction due to an adverse reaction of any grade occurred in 10% of patients

receiving neratinib plus capecitabine. Permanent discontinuation due to any adverse reaction was reported in 14% of neratinib plus capecitabine treated patients. The most common adverse reactions leading to discontinuation were vomiting (3.6%), diarrhea (2.6%), nausea (2.6%), and palmar-plantar erythrodysaesthesia syndrome (2.3%) of neratinib plus capecitabine-treated patients.

The most common adverse reactions of any grade (≥5%) in the neratinib plus capecitabine arm were diarrhea, nausea, vomiting, decreased appetite, constipation, fatigue/asthenia, weight decreased, dizziness, back pain, arthralgia, urinary tract infection, upper respiratory tract infection, abdominal distention, renal impairment, and muscle spasms. The most frequently reported Grade 3 or 4 adverse reactions were diarrhea, nausea, vomiting, fatigue, and decreased appetite.

Serious adverse reactions ≥2% in the neratinib plus capecitabine arm included diarrhea (7%), vomiting (3%), nausea (2.3%), and acute kidney injury (2.3%).

Table 11 summarizes the adverse reactions in NALA.

Table 11: Adverse Reactions Reported in ≥2% of Neratinib -Treated Patients in Combination with Capecitabine in NALA

System Organ Class (Preferred Term)	Neratinib + capecitabine n=303			Lapatinib + capecitabine n=311		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Gastrointestinal Disorders						
Diarrhea	83	25	0	66	13	0
Nausea	53	4.3	0	42	2.9	0
Vomiting	46	4	0	31	1.9	0
Constipation	31	1	0	13	0	0
Abdominal distension	8	0.3	0	3.2	0.6	0
General Disorders and Administration Site Conditions						
Fatigue/asthenia	45	6	0	40	4.5	0
Malaise	4.3	0	0	2.3	0.3	0
Influenza like illness	4	0	0	1.3	0	0
Infections and Infestations						
Urinary tract infection	9	0.7	0	4.2	0.6	0
Upper respiratory tract infection	8	0.3	0	4.5	0.3	0
Investigations						
Weight decreased	20	0.3	0	13	0.6	0
Metabolism and Nutrition Disorders						
Decreased appetite	35	2.6	0	22	2.3	0
Musculoskeletal and Connective Tissue Disorders						
Back Pain	10	0.3	0	8	0.3	0
Arthralgia	10	0	0	6	1	0

Muscle spasms	5	0	0	1.9	0	0
Nervous System Disorder						
Dizziness	14	0.3	0	10	0.6	0
Renal and urinary disorders						
Renal impairment*	7	2	0.3	1	0	0.3
Dysuria	4.6	0	0	1.9	0	0

* Renal impairment includes acute kidney injury, blood creatinine increased, renal failure, and renal impairment

Management of Diarrhea

CONTROL

The CONTROL (NCT02400476) study was a multicenter, open-label, multi-cohort trial evaluating patients with early-stage HER2-positive breast cancer treated with neratinib 240 mg daily for up to one year receiving loperamide prophylaxis with additional anti-diarrheal treatment as needed or neratinib dose escalation with loperamide as needed. All patients in the prophylaxis cohort received loperamide 4 mg loading dose, followed by 4 mg three times a day from days 1-14, followed by 4 mg twice a day on days 15-56, followed by loperamide as needed through 1 year of treatment with neratinib *[see Dosage and Administration]*. All patients in the dose escalation cohort received neratinib 120 mg for Week 1, followed by neratinib 160 mg for Week 2, followed by neratinib 240 mg for Week 3 and thereafter *[see Dosage and Administration]*.

Table 12 summarizes the diarrhea adverse reactions for neratinib with loperamide prophylaxis and neratinib dose escalation.

Table 12: Diarrhea in Patients Treated with Neratinib with Antidiarrheal Prophylaxis or Dose Escalation

	Loperamide Prophylaxis n=109	**Neratinib Dose Escalation n=60**
Duration of Treatment, months		
Median	11.8	12.0
Range	0.1, 12.8	0.2, 12.4
Dose Intensity, mg per day		
Median	234	230
Range	46, 240	32, 236
Incidence of Diarrhea, %		
Any Grade	78	98
Grade 2	25	45
Grade 3	32	13
Action Taken, %		
Discontinuation due to diarrhea	18	3.3

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:

Pusat Farmakovigilans/MESO Nasional Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif

Badan Pengawas Obat dan Makanan

Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560

Email: pv-center@pom.go.id

Website: https://e-meso.pom.go.id/ADR

Overdosage

There is no specific antidote, and the benefit of hemodialysis in the treatment of neratinib overdose is unknown. In the event of an overdose, administration should be withheld and general supportive measures undertaken.

In the clinical trial setting, a limited number of patients reported overdose. The adverse reactions experienced by these patients were diarrhea, nausea, vomiting, and dehydration. The frequency and severity of gastrointestinal disorders (diarrhea, abdominal pain, nausea and vomiting) appear to be dose related.

Clinical Pharmacology

Mechanism of Action

Neratinib is an intracellular kinase inhibitor that irreversibly binds to epidermal growth factor receptor (EGFR), HER2, and HER4. *In vitro*, neratinib reduces EGFR and HER2 autophosphorylation, downstream MAPK and AKT signaling pathways, and showed antitumor activity in EGFR and/or HER2 expressing carcinoma cell lines. neratinib human metabolites M3, M6, M7 and M11 inhibited the activity of EGFR, HER2, and HER4 *in vitro*. *In vivo*, oral administration of neratinib inhibited tumor growth in mouse xenograft models with tumor cell lines expressing HER2 and EGFR.

Pharmacodynamics

Neratinib exposure-response relationships and the time course of pharmacodynamic response are unknown.

Cardiac Electrophysiology

The effect of neratinib on the QTc interval was evaluated in a randomized, placebo, and positive-controlled, double-blind, single-dose, crossover study in 60 healthy subjects. At 140% the therapeutic exposures of neratinib, there was no clinically relevant effect on the QTc interval.

Pharmacokinetics

Neratinib AUC increases in less than dose proportional manner over a daily dose range of 40 to 400 mg.

Absorption

Peak concentrations of neratinib and major active metabolites M3, M6 and M7 are reached in the range of 2 to 8 hours after oral administration.

Effect of Food

The food-effect assessment was conducted in healthy volunteers who received neratinib 240 mg under fasting conditions and with high fat food (approximately 55% fat, 31% carbohydrate, and 14% protein) or standard breakfast (approximately 50% carbohydrate, 35% fat, and 15% protein). A high fat meal increased neratinib C_{max} and AUC_{inf} by 1.7-fold (90% CI: 1.1- 2.7) and2.2-fold (90% CI: 1.4- 3.5), respectively. A standard breakfast increased the C_{max} and AUC_{inf} by1.2-fold (90% CI: 0.97- 1.42) and 1.1-fold (90% CI: 1.02- 1.24), respectively.

Distribution

In patients, following multiple doses of neratinib, the mean (%CV) apparent volume of distribution at steady-state (Vss/F) was 6433 (19%) L. *In vitro* protein binding of neratinib in human plasma was greater than 99% and independent of concentration. neratinib bound predominantly to human serum albumin and human alpha-1 acid glycoprotein.

Elimination

Following 7 days of daily 240 mg oral doses of neratinib in healthy subjects, the mean (%CV) plasma half-life of neratinib, M3, M6, and M7 was 14.6 (38%), 21.6 (77%), 13.8 (50%) and 10.4 (33%) hours, respectively. The mean elimination half-life of neratinib ranged from 7 to 17 hours following a single oral dose in patients. Following multiple doses of neratinib at once-daily 240 mg in cancer patients, the mean (%CV) CL/F after first dose and at steady state (day 21) were 216 (34%) and 281 (40%) L/hour, respectively.

Metabolism

Neratinib is metabolized primarily in the liver by CYP3A4 and to a lesser extent by flavin-containing monooxygenase (FMO).

After oral administration of neratinib, neratinib represents the most prominent component in plasma. At steady state after 240 mg daily oral doses of neratinib in a healthy subject study (n=25), the systemic exposures (AUC) of the active metabolites M3, M6, M7 and M11were 15%, 33%, 22% and 4% of the systemic neratinib exposure (AUC) respectively.

Excretion

After oral administration of 200 mg (0.83 times of approved recommended dosage) radiolabeled neratinib oral formulation, fecal excretion accounted for approximately 97.1% and urinary excretion accounted for 1.13% of the total dose. Sixty-one percent of the excreted radioactivity was recovered within 96 hours and 98% was recovered after 10 days.

Specific Populations

Age, gender, race and renal function do not have a clinically significant effect on neratinib pharmacokinetics.

Patients with Hepatic Impairment

Neratinib is mainly metabolized in the liver. Single doses of 120 mg neratinib were evaluated in non- cancer patients with chronic hepatic impairment (n=6 each in Child Pugh Class A, B, and C) and in healthy subjects (n=9) with normal hepatic function. neratinib exposures in the patients with Child Pugh Class A (mild impairment) and Child Pugh Class B (moderate impairment) were similar to that in normal healthy volunteers. Patients with severe hepatic impairment (Child Pugh Class C) had neratinib C_{max} and AUC increased by 273% and 281%, respectively, as compared to the normal hepatic function controls. [*see Dosage and Administration*]

Non-Clinical Toxicology

Mutagenesis

Neratinib was not mutagenic in an *in vitro* bacterial reverse mutation (AMES) assay or clastogenic in an *in vitro* human lymphocyte chromosomal aberration assay or an *in vivo* rat bone marrow micronucleus assay.

Impairment of Fertility

In a fertility and early embryonic development study in female rats, neratinib was administered orally for 15 days before mating to Day 7 of pregnancy, which did not cause embryonic toxicity at doses up to 12 mg/kg/day in the presence of maternal toxicity. A dose of 12 mg/kg/day in rats is approximately 0.5 times the maximum recommended dose of 240 mg/day in patients on a mg/m^2 basis. In repeat-dose toxicity studies in dogs with oral administration of neratinib daily for up to 39 weeks, tubular hypoplasia of the testes was observed at ≥ 0.5 mg/kg/day. This finding was observed at AUCs that were approximately 0.4 times the AUC in patients at the maximum recommended dose of 240 mg.

In an embryo-fetal development study in rats, pregnant animals received oral doses of neratinib up to 15 mg/kg/day during the period of organogenesis. No effects on embryo-fetal development or survival were observed. Maternal toxicity was evident at 15 mg/kg/day (approximately 0.6 times the AUC in patients receiving the maximum recommended dose of 240 mg/day).

In an embryo-fetal development study in rabbits, pregnant animals received oral doses of neratinib up to 9 mg/kg/day during the period of organogenesis. Administration of neratinib at doses ≥6 mg/kg/day resulted in maternal toxicity, abortions, and embryo-fetal death (increased resorptions) neratinib administration resulted in increased incidence of fetal gross external (domed head), soft tissue (dilation of the brain ventricles and ventricular septal defect), and skeletal (misshapen anterior fontanelles and enlarged anterior and/or posterior fontanelles) abnormalities at ≥3 mg/kg/day. The AUC(0-t) at 6 mg/kg/day and 9 mg/kg/day in rabbits were approximately 0.5 and 0.8 times, respectively, the AUCs in patients receiving the maximum recommended dose of 240 mg/day.

In a peri- and postnatal development study in rats, oral administration of neratinib from gestation day 7 until lactation day 20 resulted in maternal toxicity at ≥10 mg/kg/day (approximately 0.4 times the maximum recommended dose of 240 mg/day in patients on a mg/m2 basis) including decreased body weights, body weight gains, and food consumption. Effects on long-term memory were observed in male offspring at maternal doses ≥5 mg/kg/day (approximately 0.2 times the maximum recommended dose of 240 mg/day in patients on a mg/m^2 basis).

Carcinogenesis

A two-year carcinogenicity study was conducted in rats at oral neratinib doses of 1, 3, and 10 mg/kg/day. neratinib was not carcinogenic in male and female rats at exposure levels >25 times the AUC in patients receiving the maximum recommended dose of 240 mg/day. Neratinib was not carcinogenic in a 26-week study in Tg.rasH2 transgenic mice when administered daily by oral gavage at doses up to 50 mg/kg/day in males and 125 mg/kg/day in females.

Clinical Studies

From Innovator Study

Extended Adjuvant Treatment of Early-Stage Breast Cancer

The safety and efficacy of neratinib were investigated in the ExteNET trial (NCT00878709), a multicenter, randomized, double-blind, placebo-controlled study of neratinib after adjuvant treatment with trastuzumab in women with HER2-positive breast cancer.

A total of 2840 patients with early-stage HER2-positive breast cancer within two years of completing treatment with adjuvant trastuzumab was randomized to receive either neratinib (n=1420) or placebo (n=1420). Randomization was stratified by the following factors: hormone receptor status, nodal status (0, 1-3 vs 4 or more positive nodes) and whether trastuzumab was given sequentially versus concurrently with chemotherapy. Neratinib 240 mg or placebo was given orally once daily for one year. The major efficacy outcome measure was invasive disease-free survival (iDFS) defined as the time between the date of randomization to the first occurrence of invasive recurrence (local/regional, ipsilateral, or contralateral breast cancer), distant recurrence, or death from any cause, with 2 years and 28 days of follow-up.

Patient demographics and tumor characteristics were generally balanced between treatment arms. Patients had a median age of 52 years (range 23 to 83) and 12% of patients were 65 or older. The majority of patients were White (81%), and most patients (99.7%) had an ECOG performance status of 0 or 1. Fifty-seven percent (57%) of patients had hormone receptor positive disease (defined as ER-positive and/or PR-positive), 24% were node negative, 47% had one to three positive nodes and 30% had four or more positive nodes. Ten percent (10%) of patients had Stage I disease, 41% had Stage II disease and 31% had Stage III disease. The majority of patients (81%) were enrolled within one year of completion of trastuzumab treatment. Median time from the last adjuvant trastuzumab treatment to randomization was 4.4 months in the neratinib arm versus 4.6 months in the placebo arm. Median duration of treatment was 11.6 months in the neratinib arm vs 11.8 months in the placebo arm.

The efficacy results from the ExteNET trial are summarized in Table 13 and Figure 1.

Table 13: Efficacy iDFS Results for the ITT Population

Number of Events/Total N (%)		iDFS at 24 months,* % (95% CI)		Stratified† HR (95% CI)	P-value‡
Neratinib	Placebo	Neratinib	Placebo		
67/1420 (4.7)	106/1420 (7.5)	94.2 (92.6, 95.4)	91.9 (90.2, 93.2)	0.66 (0.49, 0.90)	0.008

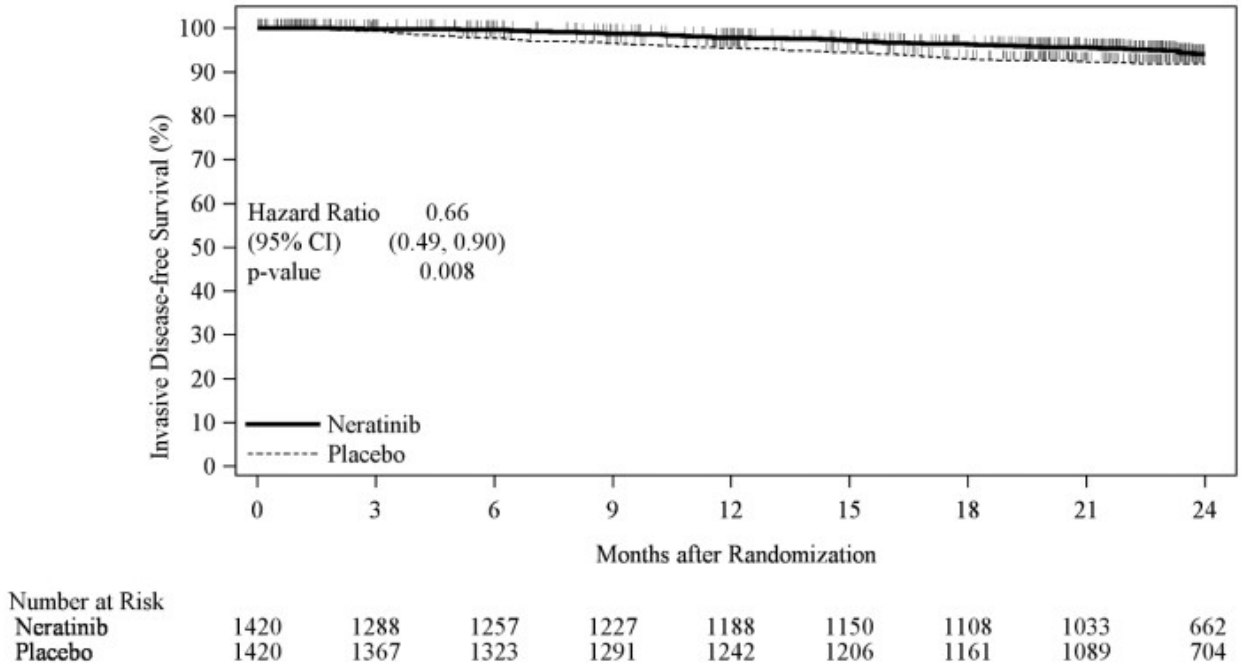
CI= Confidence Interval; HR= Hazard Ratio; iDFS= Invasive Disease Free-Survival; ITT=Intent to Treat

* Kaplan-Meier estimate

† Stratified by prior trastuzumab (concurrent vs sequential), nodal status (0–3 positive nodes vs ≥4 positive nodes), and ER/PR status (positive vs negative)

‡ Stratified log-rank test

Figure 1: iDFS in the ExteNET Trial – ITT Population



CI=Confidence Interval; iDFS=Invasive Disease Free-Survival; ITT=Intent to Treat

Table 14: Subgroup Analyses*

Population	Number of Events/Total N (%)		iDFS at 24 Months,† % (95% CI)		Unstratified HR (95% CI)
	Neratinib	Placebo	Neratinib	Placebo	
Hormone Receptor Status					
Positive	29/816 (3.6)	63/815 (7.7)	95.6 (93.8, 96.9)	91.5 (89.2, 93.3)	0.49 (0.31, 0.75)
Negative	38/604	43/605	92.2	92.4	0.93

Population	Number of Events/Total N (%)		iDFS at 24 Months,† % (95% CI)		Unstratified HR (95% CI)
	Neratinib	Placebo	Neratinib	Placebo	
	(6.3)	(7.1)	(89.4, 94.3)	(89.8, 94.3)	(0.60, 1.43)
Noda Status					
Negative	7/335 (2.1)	11/336 (3.3)	97.2 (94.1, 98.7)	96.5 (93.7, 98.0)	0.72 (0.26, 1.83)
1–3 Positive Nodes	31/664 (4.7)	47/664 (7.1)	94.4 (92.2, 96.1)	92.4 (90.0, 94.2)	0.68 (0.43, 1.07)
≥ 4 Positive Nodes	29/421 (6.9)	48/420 (11.4)	91.4 (87.9, 94.0)	87.3 (83.4, 90.2)	0.62 (0.39, 0.97)
Prior Trastuzumab					
Concurrent	49/884 (5.5)	66/886 (7.4)	93.2 (91.0, 94.8)	92.0 (89.9, 93.7)	0.80 (0.55, 1.16)
Sequential	18/536 (3.4)	40/534 (7.5)	95.8 (93.4, 97.3)	91.6 (88.7, 93.8)	0.46 (0.26, 0.78)
Completion of Prior Trastuzumab					
≤1 year	58/1152 (5.0)	95/1145 (8.3)	93.8 (92.0, 95.2)	90.9 (89.0, 92.5)	0.63 (0.45, 0.88)
1-2 years	9/262 (3.4)	11/270 (4.1)	95.8 (92.0, 97.8)	95.7 (92.3, 97.6)	0.92 (0.37, 2.22)

CI=Confidence Interval; HR=Hazard Ratio

* Exploratory analyses without adjusting multiple comparisons

† Kaplan-Meier estimate

Approximately 75% of patients were re-consented for extended follow-up beyond 24 months. Observations with missing data were censored at the last date of assessment. This exploratory analysis suggests that the iDFS results at 5 years are consistent with the 2-year iDFS results observed in ExteNET. After a median follow-up of 8 years, there was no statistically significant difference in OS between the neratinib arm and the placebo arm [HR 0.95 (95% CI: 0.75, 1.21)]. The 5-year estimate of OS was 94.1% (95% CI, 92.7%, 95.3%) in the neratinib arm and 93.3% (95% CI, 91.8%, 94.5%) in the placebo arm.

Advanced or Metastatic Breast Cancer

The safety and efficacy of neratinib in combination with capecitabine was studied in NALA (NCT01808573), a randomized, multicenter, open-label clinical trial in patients (n=621) with metastatic HER2 positive breast cancer who had received 2 or more prior anti-HER2 based regimens in the metastatic setting. HER2 expression was based on archival tissue tested at a central laboratory prior to enrollment. HER2 positivity was defined as a HER2 immunohistochemistry (IHC) score of 3+ or IHC 2+ with confirmatory in situ hybridization

(ISH) positive. Fifty-nine percent of these patients were hormone receptor positive (HR+) and 41% were hormone receptor negative (HR-); 69% had received two prior anti-HER2 based regimens, 31% had received three or more prior anti-HER2 based regimens, 81% had visceral disease, and 19% had non-visceral- only disease. Patients with asymptomatic or stable brain metastases were included in NALA trial (16%).

Patients were randomized (1:1) to receive neratinib 240 mg orally once daily on Days 1–21 in combination with capecitabine 750 mg/m2 given orally twice daily on Days 1–14 for each 21-day cycle (n=307) or lapatinib 1250 mg orally once daily Days 1–21 in combination with capecitabine 1000 mg/m2 given orally twice daily on Days 1–14 for each 21-day cycle (n=314). Patients were treated until disease progression or unacceptable toxicity.

The efficacy results from the NALA trial are summarized in Table 15, Figure 2, and Figure 3.

Table 15: Efficacy Results – NALA Trial (Central Assessment)

	Neratinib + Capecitabine (n=307)	**Lapatinib + Capecitabine (n=314)**
Progression-Free Survival (PFS)		
Number of Events (%)	210 (68.4)	223 (71.0)
Median PFS, months (95% CI)	5.6 (4.9, 6.9)	5.5 (4.3, 5.6)
HR (95% CI)*	0.76 (0.63,0.93)	
p-value†	0.0059	
PFS rates at 12 months, % (95% CI)	29 (23, 35)	15 (10, 20)
PFS rates at 24 months, % (95% CI)‡	12 (7, 18)	3 (1, 8)
Overall Survival (OS)		
Number of Events (%)	192 (62.5)	218 (69.4)
Median OS, months (95% CI)	21.0 (17.7, 23.8)	18.7 (15.5, 21.2)
HR (95% CI)*	0.88 (0.72, 1.07)	
p-value†	0.2086	
Objective Response Rate (ORR)§		
ORR, % (95% CI)	32.8 (27.1, 38.9)	26.7 (21.5, 32.4)
Duration of Response (DOR)		
Median DOR, months (95% CI)	8.5 (5.6, 11.2)	5.6 (4.2, 6.4)

HR=Hazard Ratio

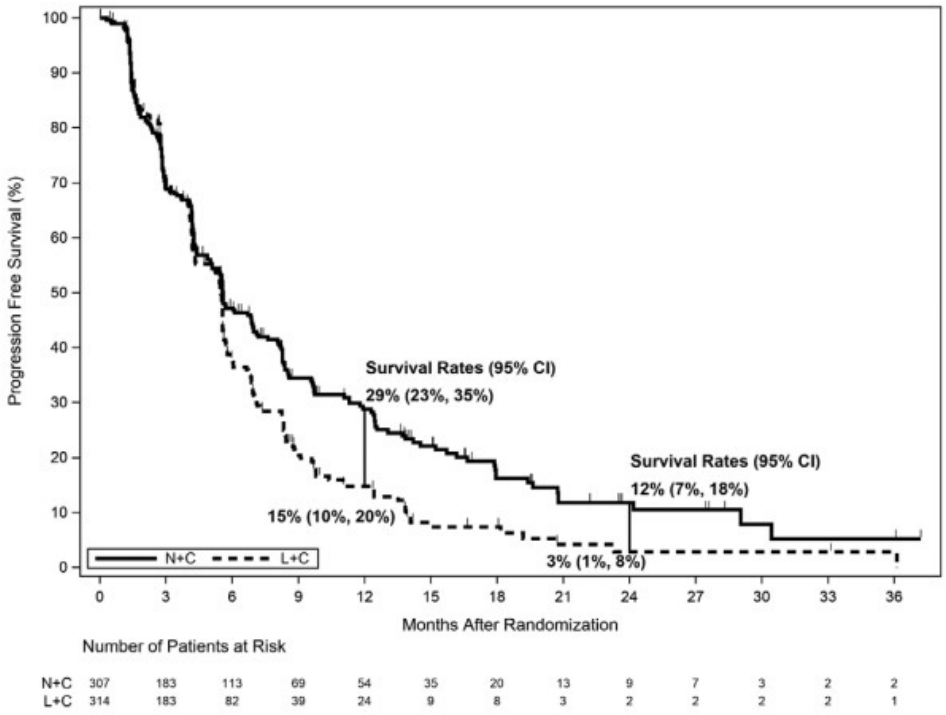
* Hazard ratio is presented as Neratinib plus Capecitabine (N+C) vs Lapatinib plus Capecitabine (L+C).

† Stratified log-rank test

‡ The total number of patients remaining on study at 24 months is 11; with 9 patients on N+C and 2 patients on L+C.

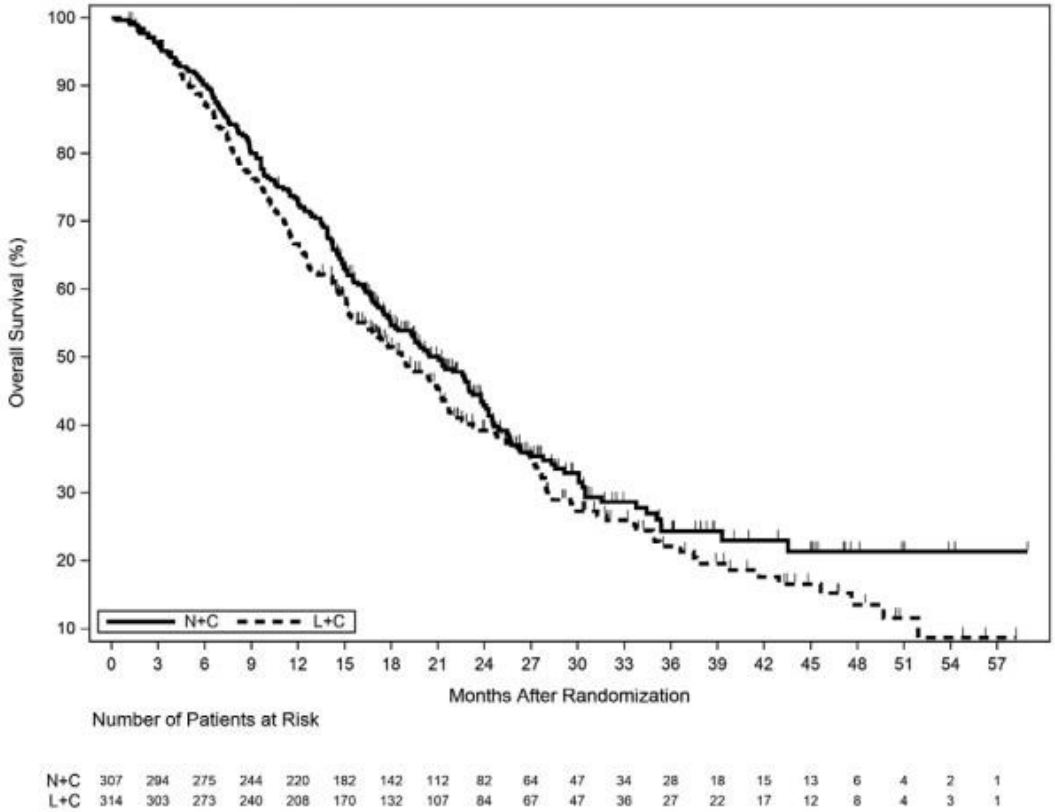
§ Confirmed ORR in patients with measurable disease at screening (256 in the N+C arm and 270 in the L+C arm).

Figure 2: Progression-Free Survival (Central Assessment - ITT Population)



CI=Confidence Interval; ITT=Intent to Treat; L+C=Lapatinib plus Capecitabine; N+C= Neratinib plus Capecitabine

Figure 3: Overall Survival (ITT Population)



ITT=Intent to Treat; L+C=Lapatinib plus Capecitabine; N+C= Neratinib plus Capecitabine

Table 16: Progression-Free Survival Rates - Subgroup Analyses[α]

Population	Number of Events/Total N (%)		PFS Rates (%) at 12 Months (95% CI)	
	Neratinib + Capecitabine	Lapatinib + Capecitabine	Neratinib + Capecitabine	Lapatinib + Capecitabine
Disease Location				
Visceral	181/247 (73.3)	185/253 (73.1)	23 (17, 30)	14 (10, 20)
Non Visceral	29/60 (48.3)	38/61 (62.3)	53 (38, 66)	18 (7, 32)
Hormone Receptor Status				
Positive	128/181 (70.7)	115/186 (61.8)	27 (19, 34)	23 (15, 31)
Negative	82/126 (65.1)	108/128 (84.4)	32 (23, 41)	5 (2, 11)
Previous HER2 regimens				
2 regimens	148/215 (68.8)	151/215 (70.2)	26 (20, 33)	13 (8, 19)
⩾3 regimens	62/92 (67.4)	72/99 (72.7)	34 (24, 45)	19 (11, 29)

CI=Confidence Interval; PFS=Progression-Free Survival

α Exploratory Analysis

Storage

Store at 25°C or below. Keep the bottle cap tightly closed to protect the tablets from moisture. The product can be used within 30 days after opening.

Packaging

Hernera: Box, 1 bottle @ 180 film-coated tablets

It is packaged in a high-density polyethylene (HDPE) bottle for oral solid preparation with a polypropylene (PP) child-resistant assemble closure, containing two 1 g silica gel desiccant of HDPE cylinder for solid preparation.

Reg. No: XXXXXXXXXXXXXX

Keep out of sight and reach of children.
Do not use this medicine after the expiry date stated on the box and label.
Keep the medicine in the original packaging.

HARUS DENGAN RESEP DOKTER

Manufactured by

2Y-Biopharma, Ltd.
Qidong, China

Registered by

PT Etana Biotechnologies Indonesia
Jakarta, Indonesia

LEMBAR INFORMASI PASIEN
HERNERA®
(neratinib maleate)
Tablet Salut Selaput

Apa itu Hernera?

- Hernera, tablet berlapis film berwarna merah berbentuk oval yang berwarna putih hingga kuning pucat setelah lapisan pelindungnya dilepas
- Hernera adalah obat resep yang digunakan tunggal untuk mengobati orang dewasa yang menderita kanker payudara stadium-awal dengan *human epidermal growth factor receptor 2 (HER2)-positive* **dan** yang sebelumnya telah diobati dengan terapi berbasis trastuzumab.
- Hernera juga digunakan dengan obat yang disebut capecitabine untuk mengobati orang dewasa yang menderita kanker payudara dengan *HER2-positive* yang telah menyebar ke bagian lain dari tubuh (metastatik) **dan** yang telah menerima 2 atau lebih obat terapi anti-HER2 untuk kanker payudara metastatik.

Tidak diketahui apakah Hernera aman dan efektif pada anak-anak.

Apa saja bahan dalam Hernera?
Bahan aktif: neratinib maleate setara dengan neratinib 40 mg
Bahan tidak aktif: bahan dasar tablet: silikon dioksida koloid, manitol, selulosa mikrokristalin, crospovidone, povidone, magnesium stearat, dan air yang dimurnikan. Lapisan tablet: lapisan film merah: polivinil alkohol, titanium dioksida, polietilen glikol, talc, dan besi oksida merah.

Apa informasi terpenting yang harus saya ketahui tentang Hernera?
Hernera dapat menyebabkan efek samping yang serius, termasuk:

- **Diare.** Diare adalah efek samping umum dari Hernera, tetapi juga bisa parah. Diare dapat menyebabkan hilangnya terlalu banyak garam dan cairan tubuh, yang dapat menyebabkan dehidrasi.
  Penyedia layanan kesehatan Anda akan meresepkan Hernera dengan salah satu dari dua cara berikut untuk membantu mengatasi diare:

  Dosis penuh Hernera:

  - Penyedia layanan kesehatan Anda akan meresepkan obat antidiare loperamide untuk Anda selama 2 bulan pertama (56 hari) pengobatan dengan Hernera dan kemudian sesuai kebutuhan. Penyedia layanan kesehatan Anda akan memberi tahu Anda dengan tepat berapa banyak dan seberapa sering minum obat ini.
  - Jika Anda diresepkan dosis penuh Hernera sejak awal pengobatan Anda, pastikan bahwa penyedia layanan kesehatan Anda juga meresepkan antidiare dengan Hernera. Anda harus mulai mengonsumsi loperamide dengan dosis pertama Hernera Anda.
  - Setelah 2 bulan (56 hari) pengobatan dengan HERNERA, ikuti instruksi penyedia layanan kesehatan Anda tentang mengonsumsi loperamide sesuai kebutuhan untuk mengendalikan diare.

  Dosis awal Hernera yang lebih rendah:

  - Penyedia layanan kesehatan Anda akan memulai Anda dengan dosis Hernera yang lebih rendah selama 2 minggu pertama pengobatan dan kemudian meningkatkan Anda ke rejimen Hernera dosis penuh. Beri tahu penyedia layanan kesehatan Anda segera jika Anda mengalami diare. Anda mungkin diresepkan loperamide sesuai kebutuhan.

  Untuk membantu mencegah atau mengurangi diare selama pengobatan dengan Hernera:

  - Penyedia layanan kesehatan Anda mungkin juga perlu memberi Anda antidiare, cairan, dan elektrolit tambahan untuk mengatasi diare saat Anda memulai pengobatan dengan Hernera. Ikuti instruksi penyedia layanan kesehatan Anda tentang cara minum obat antidiare.
  - Selalu minum antidiare persis seperti yang dikatakan oleh penyedia layanan kesehatan Anda.
  - Saat mengonsumsi antidiare, Anda dan penyedia layanan kesehatan Anda harus mencoba untuk mempertahankan jumlah buang air besar Anda pada 1 atau 2 kali buang air besar setiap hari.
  - Beri tahu penyedia layanan kesehatan Anda jika Anda megalami lebih dari 2 kali buang air besar dalam 1 hari, atau Anda mengalami diare yang tidak kunjung hilang.
  - **Hubungi penyedia layanan kesehatan Anda segera jika Anda mengalami diare parah atau jika Anda mengalami diare disertai badan lemas, pusing, atau demam.**

Penyedia layanan kesehatan Anda dapat mengubah dosis Hernera Anda, menghentikan sementara, atau menghentikan sepenuhnya Hernera jika diperlukan untuk mengatasi diare Anda.
Lihat "**Apa kemungkinan efek samping dari Hernera?"** untuk informasi lebih lanjut tentang efek samping.

Sebelum mengonsumsi Hernera, beri tahu penyedia layanan kesehatan Anda tentang semua kondisi medis Anda, termasuk jika Anda:

- berusia ≥65 tahun, karena Anda memiliki risiko lebih tinggi mengalami gangguan fungsi ginjal dan dehidrasi, terutama jika mengalami diare
- memiliki gangguan saluran cerna kronis. kondisi ini belum pernah diteliti secara khusus dalam studi utama dan perlu pengawasan lebih lanjut
- memiliki gangguan fungsi ginjal. Anda mungkin perlu dipantau secara ketat karena risiko dehidrasi akibat diare bisa meningkat
- memiliki gangguan fungsi jantung. Anda mungkin perlu dipantau secara ketat
- Memiliki keluhan pada kulit atau jaringan di bawah kulit. Anda mungkin perlu dipantau secara ketat
- memiliki gangguan hati (liver). Anda mungkin memerlukan dosis Hernera yang lebih rendah.
- sedang hamil atau berencana untuk hamil. Hernera dapat membahayakan bayi Anda yang belum lahir. Jika Anda seorang wanita yang bisa hamil:
  - Penyedia layanan kesehatan Anda harus melakukan tes kehamilan sebelum Anda mulai mengonsumsi Hernera.
  - Anda harus menggunakan kontrasepsi yang efektif selama pengobatan dan setidaknya selama 1 bulan setelah dosis terakhir Hernera Anda.
  - Beri tahu penyedia layanan kesehatan Anda tentang bentuk kontrasepsi yang dapat Anda gunakan selama waktu ini.
  - Beri tahu penyedia layanan kesehatan Anda segera jika Anda hamil selama pengobatan dengan Hernera.
  - Laki-laki dengan pasangan wanita yang dapat hamil harus menggunakan kontrasepsi yang efektif selama pengobatan dan selama 3 bulan setelah dosis terakhir Hernera.
- sedang menyusui atau berencana untuk menyusui. Tidak diketahui apakah Hernera masuk ke ASI Anda. Jangan menyusui selama pengobatan dan setidaknya selama 1 bulan setelah dosis terakhir Hernera Anda.

Beri tahu penyedia layanan kesehatan Anda tentang semua obat yang Anda minum, termasuk obat resep dan obat bebas, vitamin, dan suplemen herbal.

Terutama beri tahu penyedia layanan kesehatan Anda jika Anda menggunakan obat penurun asam lambung, seperti:

- Proton pump inhibitors (PPI), misalnya lansoprazole. Obat ini harus dihindari selama pengobatan dengan Hernera.
- Obat golongan H2-receptor antagonist, seperti ranitidine. Minum Hernera minimal 2 jam sebelum atau 10 jam setelah obat ini.
- Antasida. Minum Hernera minimal 3 jam setelah mengonsumsi antasida.

Hernera juga dapat berinteraksi dengan obat lain seperti:

- Penghambat kuat enzim CYP3A4 seperti ketoconazole, clarithromycin, dan jus grapefruit dapat meningkatkan kadar Hernera dalam tubuh dan meningkatkan risiko efek samping.
- Induktor kuat enzim CYP3A4 seperti rifampisin, phenytoin, dan St. John's wort dapat menurunkan efektivitas Hernera.

Hernera juga dapat meningkatkan kadar obat lain dalam tubuh, seperti digoxin atau dabigatran, yang dapat menyebabkan efek samping.

Konsultasikan dengan penyedia layanan kesehatan Anda sebelum memulai, menghentikan, atau mengubah dosis obat lain selama Anda menggunakan Hernera

Bagaimana saya harus mengonsumsi Hernera?

- Konsumsi Hernera persis seperti yang diminta oleh penyedia layanan kesehatan Anda.
- Penyedia layanan kesehatan Anda dapat mengubah dosis Hernera Anda jika diperlukan.
- Konsumsi Hernera dengan makanan.
- Konsumsi Hernera pada waktu yang hampir sama setiap hari.
- Telan tablet Hernera utuh. Jangan mengunyah, menghancurkan, atau membelah tablet Hernera.
- Jika Anda mengonsumsi obat antasida, minum Hernera 3 jam setelah obat antasida.
- Jika Anda mengonsumsi peredam asam (penghambat reseptor H2), Hernera harus diminum setidaknya 2 jam sebelum atau 10 jam setelah Anda minum obat-obatan ini.
- Jika Anda melewatkan dosis Hernera, lewati dosis itu dan minum dosis berikutnya pada waktu yang dijadwalkan seperti biasanya.
- Jika Anda mengonsumsi terlalu banyak Hernera, segera hubungi penyedia layanan kesehatan Anda atau pergi ke ruang gawat darurat rumah sakit terdekat.
- Hindari mengonsumsi jus grapefruit (jeruk bali) atau jus delima selama menjalani pengobatan dengan Hernera,

karena dapat memengaruhi cara kerja obat

Apa yang harus saya hindari saat mengonsumsi Hernera?
Jangan gunakan obat ini jika:

- Anda memiliki alergi terhadap zat aktif atau bahan lain yang terkandung dalam obat ini.
- Anda sedang menggunakan obat-obatan tertentu yang dapat mengganggu kerja obat ini, seperti:
  - Karbamazepin atau fenitoin (obat untuk epilepsi),
  - St John's wort (Hypericum perforatum), yaitu produk herbal yang biasa digunakan untuk mengatasi depresi ringan,
  - Rifampisin, obat untuk mengobati infeksi seperti TBC.
- Anda memiliki gangguan hati yang berat (klasifikasi Child-Pugh C).

Apa yang harus saya lakukan jika mengonsumsi Hernera lebih banyak dari yang seharusnya
Anda mungkin akan mengalami gejala diare berat, mual, muntah, dehidrasi dan nyeri perut. Segera hubungi penyedia layanan kesehatan Anda, karena Anda mungkin memerlukan penanganan medis seperti pemberian cairan dan pemantauan kondisi tubuh.

Apa kemungkinan efek samping dari Hernera?
Hernera dapat menyebabkan efek samping yang serius, termasuk:
Lihat "Apa informasi terpenting yang harus saya ketahui tentang Hernera?"

- **Gangguan hati (liver)**. Perubahan tes fungsi hati umum terjadi pada Hernera. Penyedia layanan kesehatan Anda harus melakukan tes darah sebelum Anda memulai pengobatan, setiap bulan selama 3 bulan pertama, dan kemudian setiap 3 bulan sesuai kebutuhan selama pengobatan dengan Hernera. Penyedia layanan kesehatan Anda akan menghentikan pengobatan Anda dengan Hernera jika tes fungsi hati Anda menunjukkan masalah yang parah. Hubungi penyedia layanan kesehatan Anda segera jika Anda mendapatkan salah satu tanda atau gejala masalah hati berikut:
  - kelelahan
  - mual
  - muntah
  - nyeri di area perut kanan atas
  - demam
  - ruam
  - gatal
  - kulit atau putih mata berwarna kuning

Efek samping yang paling umum Hernera bila digunakan tunggal meliputi:

- diare
- mual
- nyeri area perut
- kelelahan
- muntah
- ruam
- mulut kering atau meradang, atau sariawan
- nafsu makan menurun
- kejang otot
- sakit perut
- masalah kuku termasuk perubahan warna
- kulit kering
- pembengkakan area perut Anda
- mimisan
- penurunan berat badan
- infeksi saluran kemih

Efek samping yang paling umum Hernera bila digunakan dengan capecitabine meliputi:

- diare
- mual
- muntah
- nafsu makan menurun
- sembelit
- kelelahan/kelemahan
- penurunan berat badan
- pusing
- sakit punggung
- nyeri sendi
- infeksi saluran kemih
- infeksi saluran pernapasan atas
- pembengkakan area perut Anda
- gangguan ginjal
- kejang otot

Ini bukan semua kemungkinan efek samping dari Hernera. Untuk informasi lebih lanjut, tanyakan kepada penyedia layanan kesehatan Anda. Beri tahu penyedia layanan kesehatan Anda jika Anda memiliki efek samping yang mengganggu Anda atau yang tidak kunjung hilang.
Hubungi dokter Anda untuk mendapatkan saran medis tentang efek samping.
Anda juga dapat melaporkan efek samping melalui:
Pharmaceutical Industry Reporting Contacts
PT ETANA BIOTECHNOLOGIES INDONESIA
Kawasan Industri Pulogadung, Jl. Rawa Gelam V, Blok. L, Kav. 11-13, Jakarta
Email : pv@id.etanabiotech.com
Web-site : https://ebi-pharmacovigilance.azurewebsites.net/

Bagaimana cara menyimpan Hernera?

- Simpan pada suhu ≤ 25 C. Tutup rapat botol untuk mencegah kelembapan.
- Produk dapat digunakan dalam waktu 30 hari setelah kemasan dibuka.

Jauhkan Hernera dan semua obat-obatan dari jangkauan anak-anak.

Informasi umum tentang penggunaan Hernera yang aman dan efektif.

Jangan gunakan Hernera untuk kondisi yang tidak diresepkan. Jangan memberikan Hernera kepada orang lain, bahkan jika mereka memiliki gejala yang sama yang Anda miliki. Hal ini bisa membahayakan mereka. Anda dapat meminta apoteker atau penyedia layanan kesehatan Anda untuk informasi tentang Hernera yang ditulis untuk tenaga profesional kesehatan.

HARUS DENGAN RESEP DOKTER

No. Reg: XXXXXXXXXXXXX

Dus, 1 botol @ 180 tablet salut selaput

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