NATIONAL PHARMACEUTICAL REGULATORY DIVISION MINISTRY OF HEALTH MALAYSIA

TECHNICAL EVALUATION SUMMARY

PRODUCT NAME:
NERLYNX (neratinib) Film-Coated Tablets 40 mg (MAL20076009ACRZ)

ACTIVE INGREDIENT:
Neratinib maleate 48.31 mg (equivalent to 40 mg of neratinib free base)

PRODUCT REGISTRATION HOLDER:
Pharma To Market Sdn. Bhd., Malaysia.

PRODUCT MANUFACTURER:
Contract manufacturer & primary packager: Excella GmbH & Co. KG, Germany
Secondary packager & batch release: Zuellig Pharma Specialty Solutions Group Pte. Ltd., Singapore
[Product owner: Puma Biotechnology, Inc., United States]

APPROVAL DATE:
9th July 2020 (DCA 346)

1.0 BACKGROUND INFORMATION

1.1 Approved Indication

NERLYNX is indicated for the extended adjuvant treatment of women with early-stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than one year ago.

1.2 Approved Posology

Antidiarrheal Prophylaxis

Antidiarrheal prophylaxis is recommended during the first 2 cycles (56 days) of treatment and should be initiated with the first dose of NERLYNX.

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

Table 1: Loperamide Prophylaxis

Time on NERLYNX	Dose	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)

NERLYNX dose interruptions and dose reductions may also be required to manage diarrhea.

Recommended Dose and Schedule

The recommended dose of NERLYNX is 240 mg (six tablets) given orally once daily with food, continuously for one year.

Instruct patients to take NERLYNX at approximately the same time every day. NERLYNX 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 NERLYNX with the next scheduled daily dose.

Dose Modifications

Dose Modifications for Adverse Reactions

NERLNX 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 2 to Table 5. Discontinue NERLYNX for patients who fail to recover to Grade 0-1 from treatment-related toxicity, for toxicities that result in a treatment delay > 3 weeks, or for patients that are 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.).

Table 2: NERLYNX Dose Modifications for Adverse Reactions

Dose Level	**NERLYNX 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 3: NERLYNX Dose Modifications and Management – General Toxicities[1]

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

1 Refer to Table 4 and Table 5 below for management of diarrhea and hepatotoxicity

2 Per CTCAE v4.0

Dose Modifications for Diarrhea

Diarrhea management requires the correct use of antidiarrheal medication, dietary changes, and appropriate dose modifications of NERLYNX. Guidelines for adjusting doses of NERLYNX in the setting of diarrhea are shown in Table 4.

Table 4: Dose Modifications for Diarrhea

Severity of Diarrhea[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 1 or baseline, start loperamide 4 mg with each subsequent NERLYNX 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 NERLYNX 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 NERLYNX treatment at the same dose • If diarrhea resolves to Grade 0-1 in longer than one week, then resume NERLYNX treatment at reduced dose (see Table 2) • Once event resolves to ≤ Grade 1 or baseline, start loperamide 4 mg with each subsequent NERLYNX administration.
• Grade 4 diarrhea [Life-threatening consequences; urgent intervention indicated]	• Permanently discontinue NERLYNX treatment
• Diarrhea recurs to Grade 2 or higher at 120 mg per day	• Permanently discontinue NERLYNX 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 Hepatic Impairment

Reduce the NERLYNX starting dose to 80 mg in patients with severe hepatic impairment (Child Pugh C). No dose modifications are recommended for patients with mild to moderate hepatic impairment (Child Pugh A or B).

Dose Modifications for Hepatotoxicity

Guidelines for dose adjustment of NERLYNX in the event of liver toxicity are shown in Table 5. Patients who experience ≥ Grade 3 diarrhea requiring IV fluid treatment 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.

Table 5: Dose Modifications for Hepatotoxicity

Severity of Hepatotoxicity[1]	**Action**
• Grade 3 ALT (>5-20x ULN) OR • Grade 3 bilirubin (>3-10x ULN)	• Hold NERLYNX until recovery to ≤ Grade 1 • Evaluate alternative causes • Resume NERLYNX 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 NERLYNX
• Grade 4 ALT (>20x ULN) OR • Grade 4 bilirubin (>10x ULN)	• Permanently discontinue NERLYNX • Evaluate alternative causes

1 Per CTCAE v4.0

Concomitant Use with Gastric Acid Reducing Agents

Proton pump inhibitors (PPI): Avoid concomitant use with NERLYNX.

H_2-receptor antagonists: Take NERLYNX at least 2 hours before the next dose of the H_2-receptor antagonist or 10 hours after the H_2-receptor antagonist.

Antacids: Separate dosing of NERLYNX by 3 hours after antacids.

1.3 Method of administration

NERLYNX tablets should be swallowed whole (tablets should not be chewed, crushed, or split prior to swallowing).

1.4 Pharmacological Aspects

Mechanism of Action

Neratinib is a kinase inhibitor that irreversibly binds Epidermal Growth Factor Receptor (EGFR), Human Epidermal Growth Factor Receptor 2 (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.

Cardiac Electrophysiology

The effect of NERLYNX on the QTc interval was evaluated in a randomized, placebo and positive controlled, double-blind, single-dose, crossover study in 60 healthy subjects. At 2.4-fold the therapeutic exposures of NERLYNX, there was no clinically relevant effect on the QTc interval.

2.0 SUMMARY REPORT

2.1 Quality

2.1.1 Active Pharmaceutical Ingredient (API)

- Overall the quality of API are in accordance with International Council for Harmonization (ICH) and World Health Organization (WHO) guidelines and have been assessed to meet the regulatory requirements.
- Anhydrate Form I polymorph was consistently produced by the manufacturing process. The proposed starting materials have been adequately justified in line with ICH Q11 (*Guideline on Development and Manufacturer of Drug Substance*) and acceptable specifications have been set. The manufacturing process of neratinib maleate was sufficiently described and adequate in-process controls are applied during the manufacturing process. Acceptable specifications and control methods for intermediate products, starting materials and reagents have been presented.

- The characterisation of the API and its impurities are in accordance with the EMA Guideline on *Chemistry of New Active Substances.*
- The specification of API is controlled in accordance to the in-house requirements. The proposed acceptance criterion for impurity is in accordance with ICH Q3A (*Guideline on Impurities in New Drug Substances*). Batch analysis data for three batches were provided and the results were within the proposed specifications.
- The analytical methods used have been appropriately validated in accordance with ICH Q2(R1) (*Validation of Analytical Procedures: Text and Methodology*) guidelines.
- The stability studies on four batches were performed for 6 months at 40±2°C/75± 5%RH, one batch was performed for 24 months at 25±2°C/60±5%RH and three batches were performed for 18 months at 25±2°C/60±5%RH. The results of stability data showed that the API remains within the specification. The stability studies were conducted in accordance with ICH Q1 (*Guideline on Stability Testing of New Drug Substances and Products*).
- The proposed re-test period is 24 months when stored below 25°C in an inner transparent linear low-density polyethylene (LLDPE)/low-density polyethylene (LDPE) bag, placed inside an outer complex laminated thermoseal and further placed inside a metallic drum.

2.1.2 Finished Product

- The manufacturing process has been validated and the results fulfilled the expected acceptance criteria proving that the finished product manufacturing processes are robust and reproducible.
- The stability studies data support a shelf life of 36 months when stored below 30°C. The 36 months long-term stability data at 30±2°C/75±5%RH and 6 months accelerated stability data at 40±2°C/75±5%RH for three stability batches remained well within specifications. Photostability study was performed and showed that the drug product is photostable in the proposed immediate packaging.
- The product has passed the evaluation on analytical protocol and method validation in accordance with the ICH Q2 (R1) guidelines.
- Certificate of GMP Compliance for the manufacturer was issued by the Central Authority of the Laender for Health Protection regarding Medical Products and Medical Devices, Germany.

2.2 Efficacy

The safety and efficacy of neratinib for the proposed indication has been established in Phase III pivotal Study 3144A2-3004-WW (also known as Extended Adjuvant Treatment of Breast Cancer with Neratinib [ExteNET]), a multicentre, randomised, double-blind, placebo-controlled trial of one

year of neratinib versus placebo in women with early stage HER-2 positive breast cancer after adjuvant treatment with trastuzumab.

Summary of Clinical Study Conducted

Study type & design (N)	Objective of the study	Key results
Study 3144A2-3004-WW (ExteNET) [Martin M*, et al. Lancet Oncology,* 2017] Phase III, randomised, double-blind, placebo-controlled, multicentre study N=2840 Women aged ≥18 years [≥20 years in Japan] with histologically confirmed stage 2-3c HER2-positive operable breast cancer, who had completed neoadjuvant and adjuvant chemotherapy plus trastuzumab with no evidence of disease recurrence or metastasis	To investigate extended adjuvant therapy with neratinib or placebo given for 1 year following standard trastuzumab-based adjuvant therapy in women with early-stage HER2-positive breast cancer	• The primary analysis at 2 years after randomisation showed that the number of patients with invasive disease-free survival (iDFS) event was significantly lower in the neratinib group than the placebo group (67 vs 106 events; stratified HR 0.66, 95% CI: 0.49, 0.90, p=0.008). • At 5 years after randomisation, patients in the neratinib group also had significantly fewer iDFS events than patients in the placebo group (116 vs 163 events; stratified HR 0.73, 95% CI: 0.57, 0.92, p=0.0083). • In the subgroup of patients with hormone receptor-positive disease, the HR for iDFS in neratinib group compared with the placebo group was 0.60 (95% CI: 0.43, 0.83), whereas in the patients with hormone receptor-negative disease, the HR for iDFS was 0.95 (95% CI: 0.66, 1.35) • The overall survival (OS) data is not yet mature. Conclusion: Neratinib administered for 1 year after completion of trastuzumab-based adjuvant therapy significantly improved 2-year iDFS in women with early-stage

Study type & design (N)	Objective of the study	Key results
Age (median): Neratinib: 52 years (Range: 45–59) Placebo: 52 years (Range: 45–60) Duration of treatment (median): Neratinib: 353 days Placebo: 360 days		HER2-positive breast cancer. The improvement in iDFS remains durable for up 5 years. Prospectively defined subgroup analyses indicated greater benefit in patients with hormone receptor-positive disease.

2.3 Safety

- The most frequently reported treatment-emergent adverse events (TEAEs) of grade 3 or 4 in the neratinib group and placebo group, respectively, were diarrhea (562 [39.9%], 23 [1.6%]), vomiting (47 [3.3%], 5 [0.4%]), nausea (26 [1.8%], 2 [0.1%]), abdominal pain (24 [1.7%], 3 [0.2%]), fatigue (23 [1.6%], 6 [0.4%], and alanine aminotransferase (ALT) increased (18 [1.3%], 3 [0.2%]). There was only 1 grade 4 diarrhea in the neratinib arm versus 0 in the placebo arm, and 3 patients were reported with a Grade 4 ALT increased in the neratinib arm versus 0 in the placebo arm.
- Serious TEAEs occurred in 103 (7%) patients in the neratinib group and 85 (6%) patients in the placebo group. The most common serious adverse events in the neratinib group versus placebo group were diarrhea (22 [1.6%], 1 [0.1%]), vomiting (12 [0.9%], 1 [0.1%]) and dehydration (9 [0.6%], 1 [0.1%]).
- Most patients in the neratinib group (93.0%) experienced diarrhea in the first month of treatment (median time to first onset was 2 days) and the incidence decreased to approximately 50% in each subsequent month. Diarrhea was generally manageable with conventional therapy, most frequently loperamide (85.1%) and neratinib dose reductions or discontinuations.

- The 1-year course of neratinib is not associated with long-term toxicities, specifically increased symptomatic cardiac toxicity or second primary malignancies.

3.0 CONCLUSION

Drug Control Authority (DCA) on the 346th meeting on 9th July 2020 has decided to approve the registration of this product with the following indication:

NERLYNX is indicated for the extended adjuvant treatment of women with early-stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than one year ago.