Tambahan Indikasi yang diluluskan dalam Mesyuarat PBKD 388, 14 September 2023

Products approved for additional indication (DCA 388 – 14 September 2023)

<table>
<tr><th>No.</th><th>Product
[Active Ingredient]</th><th>Additional Indication</th><th>Product Registration Holder (PRH)</th></tr>
<tr><td>1.</td><td>NERLYNX (neratinib) Film-Coated Tablets 40 mg

[Neratinib maleate 48.31 mg (equivalent to 40 mg of neratinib free base)]</td><td>
INDICATION :

1.2 Advanced or Metastatic Breast Cancer

NERLYNX in combination with capecitabine is indicated 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 [see Clinical Studies (13.2)].

POSOLOGY :

Advanced or Metastatic Breast Cancer

The recommended dose of NERLYNX 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.

<u>Dose Escalation</u>

A two-week dose escalation for NERLYNX 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 (5.1) and Adverse Reactions (6.1)].

Table 2: NERLYNX Dose Escalation and Treatment Schedule
<table>
<tr><th>Time on NERLYNX</th><th>NERLYNX Dose</th></tr>
<tr><td>Week 1 (days 1 – 7)</td><td>120 mg daily (three 40 mg tablets)</td></tr>
<tr><td>Week 2 (days 8 – 14)</td><td>160 mg daily (four 40 mg tablets)</td></tr>
<tr><td>Week 3 and onwards</td><td>240 mg daily (six 40 mg tablets, recommended dose)</td></tr>
</table>
</td><td>ZUELLIG PHARMA SDN. BHD.
No. 15, Persiaran Pasak Bumi, Sek. U8, Perindustrian Bukit Jelutong,
40150 Shah Alam, Selangor.</td></tr>
</table>

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If diarrhea occurs, treat with antidiarrheal medications, fluids, and electrolytes as clinically indicated.

NERLYNX dose interruptions and dose reductions may also be required to manage diarrhea [see Dosage and Administration (2.3)].

Dosage Modifications for Adverse Reactions

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

Table 5: NERLYNX in Combination with Capecitabine Dose Modifications for Adverse Reactions
<table>
<tr><th>Dose Level</th><th>NERLYNX Dose</th></tr>
<tr><td>Recommended starting dose</td><td>240 mg daily (six 40 mg tablets)</td></tr>
<tr><td>First dose reduction</td><td>160 mg daily (four 40 mg tablets)</td></tr>
<tr><td>Second dose reduction</td><td>120 mg daily (three 40 mg tablets)</td></tr>
</table>
Table 6: Recommended Dosage Modifications for Adverse Reactions with NERLYNX in Combination with Capecitabine
<table>
<tr><th>Adverse Reaction</th><th>Severity†</th><th>Action/Dose Modification</th></tr>
</table>
</td><td></td></tr>
</table>

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No.	Product [Active Ingredient]	Additional Indication			Product Registration Holder (PRH)
		Diarrhea [see Warnings and Precautions (5.1)]	• 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 NERLYNX and capecitabine at full doses • Diet modifications • Fluid intake of ~2L/day should be maintained to avoid dehydration • Once the event resolves to Grade ≤1 or baseline, start loperamide 4 mg with each subsequent NERLYNX administration.	

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No.	Product [Active Ingredient]	Additional Indication				Product Registration Holder (PRH)
			• 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 NERLYNX and capecitabine until recovery to Grade ≤1 or baseline • Diet modifications • Fluid intake of ~2L/day should be maintained intravenously, if needed • If recovery occurs: o ≤1 week after withholding treatment, resume same doses of NERLYNX and capecitabine o Within 1 – 3 weeks after withholding treatment, reduce NERLYNX dose to 160 mg and maintain the same dose of capecitabine. • If event occurs a second time and the NERLYNX dose has not already been decreased, reduce NERLYNX dose to 160 mg (maintain the same dose of capecitabine). If NERLYNX 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	

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No.	Product [Active Ingredient]	Additional Indication			Product Registration Holder (PRH)
				NERLYNX). • If subsequent events occur, reduce the dose of NERLYNX 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 NERLYNX was previously reduced, or reduce NERLYNX to 120 mg if capecitabine was previously reduced) • Once the event resolves to Grade ≤1 or baseline, start loperamide 4 mg with each subsequent NERLYNX administration	
		Hepatotoxicity [see Warnings and Precautions (5.2)]	• Grade 3 ALT or AST (>5 – 20 x ULN) OR • Grade 3 bilirubin (>3 – 10 x 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 AST, or bilirubin occurs again despite one dose reduction, permanently discontinue NERLYNX	

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No.	Product [Active Ingredient]	Additional Indication			Product Registration Holder (PRH)
			• Grade 4 ALT or AST (>20 x ULN) OR • Grade 4 bilirubin (>10 x ULN)	• Permanently discontinue NERLYNX • Evaluate alternative causes	
			Other [see Adverse Reactions (6.1)]	• 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

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.

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No.	Product [Active Ingredient]	Additional Indication	Product Registration Holder (PRH)
2.	Xarelto 20 mg film-coated tablet [Rivaroxaban 20mg] Xarelto 15 mg film-coated tablet [Rivaroxaban 15mg]	**INDICATION :** Paediatric population Xarelto 15 mg Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing from 30kg to 50 kg after at least 5 days of initial parenteral anticoagulation treatment. Xarelto 20 mg Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing more than 50 kg after at least 5 days of initial parenteral anticoagulation treatment. **POSOLOGY :** Treatment of VTE and prevention of VTE recurrence in children and adolescents Xarelto treatment in children and adolescents aged less than 18 years should be initiated following at least 5 days of initial parenteral anticoagulation treatment. The dose for children and adolescent is calculated based on body weight. – Body weight of 50 kg or more: a once daily dose of 20 mg rivaroxaban is recommended. This is the maximum daily dose. – Body weight from 30 to 50 kg: a once daily dose of 15 mg rivaroxaban is recommended. This is the maximum daily dose. The weight of a child should be monitored and the dose reviewed regularly. This is to ensure a therapeutic dose is maintained. Dose adjustments should be made based on	**BAYER CO. (MALAYSIA) SDN. BHD.** 25-03 & 25-04, Level 25, Imazium, No. 8, Jalan SS21/37, Damansara Uptown, 47400 Petaling Jaya, Selangor.

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No.	Product [Active Ingredient]	Additional Indication	Product Registration Holder (PRH)
		changes in body weight only. Treatment should be continued for at least 3 months in children and adolescents. Treatment can be extended up to 12 months when clinically necessary. There is no data available in children to support a dose reduction after 6 months treatment. The benefit-risk of continued therapy after 3 months should be assessed on an individual basis taking into account the risk for recurrent thrombosis versus the potential bleeding risk. If a dose is missed, the missed dose should be taken as soon as possible after it is noticed, but only on the same day. If this is not possible, the patient should skip the dose and continue with the next dose as prescribed. The patient should not take two doses to make up for a missed dose. Converting from Vitamin K Antagonists (VKA) to Xarelto - Prevention of stroke and systemic embolism: VKA treatment should be stopped and Xarelto therapy should be initiated when the International Normalized Ratio (INR) is ≤ 3.0. - Treatment of DVT, PE and prevention of recurrence in adults and treatment of VTE and prevention of recurrence in paediatric patients: VKA treatment should be stopped and Xarelto therapy should be initiated once the INR is ≤ 2.5. When converting patients from VKAs to Xarelto, INR values will be falsely elevated after the intake of Xarelto. The INR is not valid to measure the anticoagulant activity of Xarelto, and therefore should not be used. Paediatric patients: Children who convert from Xarelto to VKA need to continue Xarelto for 48 hours after the first dose of VKA. After 2 days of co-administration an INR should be obtained prior to the next scheduled dose of Xarelto. Co-administration of Xarelto and VKA is advised to continue until the INR is ≥ 2.0. Once Xarelto is discontinued INR testing may be done reliably 24 hours after the last dose.	

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No.	Product [Active Ingredient]	Additional Indication	Product Registration Holder (PRH)
		Converting from parenteral anticoagulants to Xarelto For adult and paediatric patients currently receiving a parenteral anticoagulant, discontinue the parenteral anticoagulant and start Xarelto 0 to 2 hours before the time that the next scheduled administration of the parenteral medicinal product (e.g. low molecular weight heparins) would be due or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin). Paediatric population: ▪ Children and adolescents with mild renal impairment (glomerular filtration rate 50 - 80 mL/min/1.73 m2): no dose adjustment is required, based on data in adults and limited data in paediatric patients. ▪ Children and adolescents with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m2): Xarelto is not recommended as no clinical data is available. Hepatic impairment Xarelto is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C. No clinical data is available in children with hepatic impairment. Body weight No dose adjustment for adults. For paediatric patients the dose is determined based on body weight. Paediatric population The safety and efficacy of Xarelto in children aged 0 to < 18 years have not been established in the indication prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. No data are available. Therefore, it is not recommended for use in children below 18 years of age in indications other than the treatment of VTE and prevention of VTE recurrence.	

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No.	Product [Active Ingredient]	Additional Indication	Product Registration Holder (PRH)
		Method of administration Children and adolescents weighing 30kg to 50 kg Xarelto is for oral use. The patient should be advised to swallow the tablet with liquid. It should also be taken with food. The tablets should be taken approximately 24 hours apart. In case the patient immediately spits up the dose or vomits within 30 minutes after receiving the dose, a new dose should be given. However, if the patient vomits more than 30 minutes after the dose, the dose should not be re-administered and the next dose should be taken as scheduled. The tablet must not be split in an attempt to provide a fraction of a tablet dose. Crushing of tablets For patients who are unable to swallow whole tablets, Xarelto granules for oral suspension should be used. If the oral suspension is not immediately available, when doses of 15 mg or 20 mg rivaroxaban are prescribed, these could be provided by crushing the 15 mg or 20 mg tablet and mixing it with water or apple puree immediately prior to use and administering orally. The crushed tablet may be given through a nasogastric or gastric feeding tube.	