The **carry-over** effect in breast cancer: **sustained benefits** of early treatment

The carry-over effect in early breast cancer (EBC) treatment refers to the sustained reduction in recurrence and mortality risk that persists well beyond the completion of adjuvant treatments. The effect highlights the profound impact of early interventions in shaping long-term outcomes, particularly for patients with hormone receptor (HR)-positive EBC. Furthermore, it underlines the importance of adhering to prescribed adjuvant treatments. In this article, **Prof. Dr. François Duhoux** (Cliniques universitaires Saint-Luc, Brussels) and **Prof. Dr. Patrick Neven** (University Hospitals Leuven, Leuven) discuss the carry-over effect seen with adjuvant treatments, and the implications for daily clinical practice.

The carry-over effect related to endocrine therapy (ET)

The term 'carry-over effect' is used to describe the long-lasting benefit of adjuvant treatments in reducing the risk of recurrence after stopping the initial treatment. It has been observed with adjuvant ET, such as tamoxifen and aromatase inhibitors, which is the standard of care for patients with HR-positive, human epidermal growth factor 2 (HER2)-negative EBC.[1] The term was first used to describe the persistent benefit of adjuvant tamoxifen beyond five years after completion of treatment.[2] An EBCTCG analysis showed that five years of adjuvant tamoxifen safely reduced 15-year risks of breast cancer recurrence and death.[3] Breast cancer mortality was reduced by about a third throughout the first 15 years.[3] Furthermore, extending adjuvant tamoxifen beyond five years led to a further reduction in recurrence and mortality.[4] In addition, an EBCTCG analysis showed that adjuvant therapy with five years of aromatase inhibitors *vs* five years of tamoxifen was more effective in preventing recurrence and breast cancer mortality, and the absolute benefit was greater years after than during therapy.[5]

However, many recurrences still occur after five years of adjuvant ET. A meta-analysis showed that in patients with HR-positive disease who were disease-free after five years of ET, the risk of recurrence continued to occur steadily throughout the study period from five to 20 years.[6] In addition, the risk of distant recurrence was strongly correlated with the original tumour diameter and nodal status.[6] Also, in patients with high-risk HR-positive HER2-negative EBC, the risk of recurrence is three times higher than in patients with non-high-risk disease, and ~30% of high-risk patients may experience disease recurrence in five years.[7]

Therefore, it is important for clinicians to be aware about and to understand the carry-over effect seen with adjuvant treatments. Treatment duration, treatment adherence and treatment choice may impact the carry-over effect. It is important to provide patient-tailored treatment aiming to reduce the risk of disease recurrence, especially metastatic disease.

How common is a carry-over effect of treatment in breast cancer?

Prof. Dr. Duhoux: "The effect was first observed with ET, initially with tamoxifen. Studies showed that ET for HR-positive breast cancer had enduring effects. Survival curves continued to diverge between patients who received tamoxifen and those who did not, ever after the treatment was discontinued. This carry-over effect has recently also been demonstrated with cyclin dependent kinase 4 or 6 inhibitors (CDK4/6i), more particularly abemaciclib."

Prof. Dr. Neven: "Indeed, the carry-over effect is a well-documented phenomenon with ET, with its impact often extending well beyond the active treatment period. We have observed it with tamoxifen years ago, with a persistent benefit of adjuvant tamoxifen beyond five years after completion of treatment. Similarly, it was observed with oral aromatase inhibitors, with an additional reduction in risk of recurrence compared to tamoxifen. Also, this was seen in several breast cancer tamoxifen prevention trials, but also with anastrozole over a period of years of follow-up where the aromatase inhibitor was given for five years.[8] Furthermore, it is also evident with immunotherapy and, more recently, it has been demonstrated with the

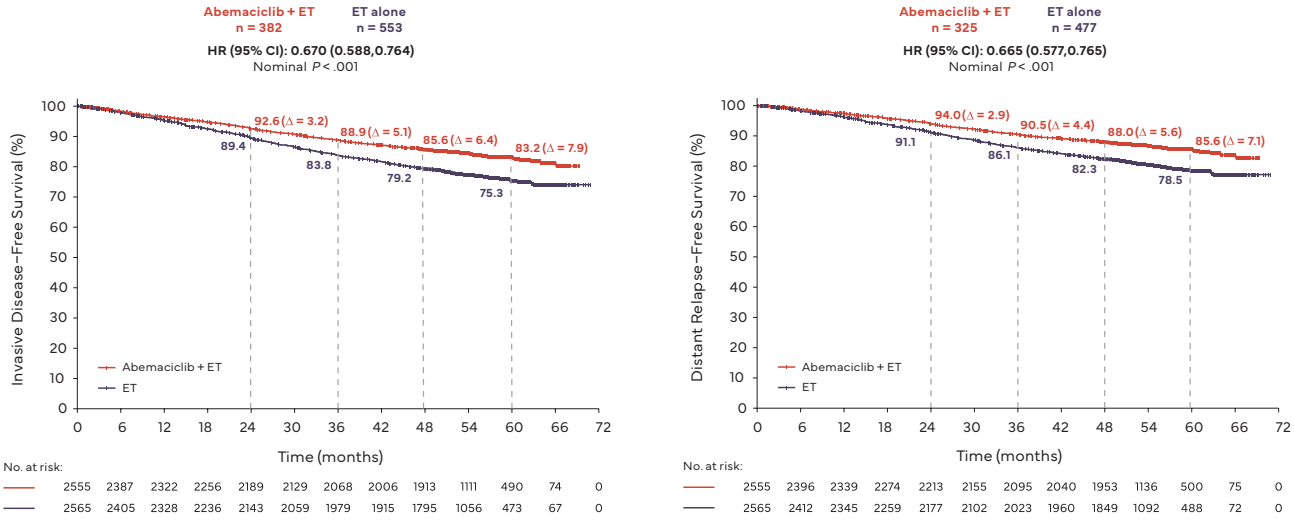

Figure 1. Kaplan-Meier survival curves of **(A)** invasive disease-free survival and **(B)** distant relapse-free survival in cohort 1 of the monarchE study at a median follow-up of 54 months.[11]

Cohort 1 includes patients with ≥4 positive pathologic axillary lymph nodes, or 1-2 positive pathologic lymph nodes with additional high-risk features of either grade 3 disease or tumour size ≥5 cm.

CI= confidence interval; ET= endocrine therapy; HR= hazard ratio.

CDK4/6i abemaciclib in the monarchE study. The biology of the carry-over effect in adjuvant treatments for EBC involves the sustained impact of therapies beyond their active administration, and a key concept in understanding this effect is the dormancy of cancer cells. Adjuvant therapies such as ET may either eradicate these dormant cells or maintain them in a non-proliferative status, reducing the risk of recurrence long after the active treatment period ends. It must be in HR-positive breast cancer, that adjuvant ET deprives dormant hormone-sensitive cells of the signals needed to reactivate and proliferate. In contrast, the stimulating effect of menopausal hormones on the appearance of HR-positive breast cancer stops once the hormone replacement ends.[9]"

Can you tell us more about the carry-over effect seen with abemaciclib, and how relevant this is for you as a clinician?

Prof. Dr. Duhoux: "For the clinician, it is important to see that the efficacy of a prescribed adjuvant treatment is sustained after its discontinuation. When data from trials involving CDK4/6i in the adjuvant setting became available, many oncologists initially believed these treatments targeted undetected (micro-)metastatic disease and that the survival curves would converge after treatment cessation. However, this was not observed, indicating that disease recurrence is significantly delayed in some patients. This is particularly relevant in HR-positive HER2-negative breast cancer, when recurrences can occur even decades after the initial diagnosis. In patients with more aggressive tumours, such as those enrolled in the monarchE trial, recurrences typically occur earlier. Therefore, five years of follow-up for this high-risk patient group represents a significant milestone and is an essential consideration in clinical decision-making."

Prof. Dr. Neven: "In the abemaciclib arm of cohort 1 of the monarchE study, the two-year and five-year invasive disease-free survival (iDFS) rates were 92.6% and 83.2%, respectively, with an absolute difference of 9.4% between these time points. In the control arm, the iDFS rates were 89.4% at two years and 75.3% at five years, showing a larger absolute difference of 14.1%. The absolute difference between the treatment arms was 3.2% at two years and 7.9% at five years. For distant relapse-free survival (DRFS), the two-year and five-year rates in the abemaciclib arm were 94.0% and 85.6% (absolute difference between time points 8.4%), compared to 91.1% and 78.5% in the control arm (absolute difference between time points 12.6%). The absolute difference between treatment arms was 2.9% at two years and 7.1% at five years. These findings demonstrate the widening of the survival curves over time with abemaciclib. In monarchE, approximately 80% of patients have been off treatment for at least two years and the median follow-up is 54 months. For clinicians, the carry-over effect may serve as a better predictor of overall survival (OS) benefit. However, OS data from monarchE are not yet available and will still take several years to mature. Nonetheless, the increasing benefit over time in iDFS and DRFS provides reassuring evidence of the long-term efficacy of abemaciclib."

Do you expect to see the same carry-over effect with other CDK4/6i?

Prof. Dr. Duhoux: "We do not expect to observe this effect with palbociclib, as the adjuvant trials for palbociclib yielded

negative results. However, we hope to see the carry-over effect with ribociclib, as demonstrating this effect is important. It provides reassurance that the added toxicity associated with the treatment was justified."

Prof. Dr. Neven: "I agree and do expect seeing this effect with ribociclib in the NATALEE trial, but it is still too early to confirm this due to the shorter follow-up at this moment. We did not see the carry-over effect with palbociclib, as the curves did not separate."

Is the carry-over effect something you discuss with your patients as well? Does it help them in being treatment adherent?

Prof. Dr. Duhoux: "I rarely bring this up at the start of treatment, but I do discuss it later to reassure the patients when they stop their treatment after a certain treatment period. Interestingly, some patients would actually like to continue because they feel protected by the drug."

Prof. Dr. Neven: "Yes, this is reassuring for the patient. You can explain that the additional two years of treatment are well worth it, despite the associated toxicity, as the benefit persists even three years after stopping the treatment. While the treatment can be quite toxic, particularly during the initial cycles – diarrhoea being a common side effect – it is important to discuss these challenges with the patients. Additionally, approximately half of the patients require dose adjustments due to adverse events, but even for those who undergo dose reductions, the carry-over effect remains evident."

Which endpoints are most relevant to take into account when speaking about the carry-over effect?

Prof. Dr. Duhoux: "For patients with early-stage disease, DRFS is the most important intermediate endpoint. The gold standard still remains OS, but we don't expect to have OS data for patients treated with adjuvant CDK4/6i in the coming years."

Prof. Dr. Neven: "Endpoints related to metastatic disease are more important because these are likely related to OS. Therefore, DRFS is more important than *e.g.* loco-regional relapse."

Finally, do you recommend the addition of abemaciclib to ET for all patients with HR-positive, HER2-negative, node-positive, high-risk EBC?

Prof. Dr. Duhoux: "Well, I use it for nearly all patients in this setting, except for those who are very frail or elderly with a poor oncogeriatric score. I would administer abemaciclib to all other patients, *i.e.* those with more than four positive lymph nodes or one to three positive lymph nodes with either grade 3 disease or a tumour size of at least 5 cm."

Prof. Dr. Neven: "First of all, the patient needs to fulfil the reimbursement criteria. If all reimbursement criteria are present, the treatment is discussed with the patients and proposed to the patients with a good performance status."

Background information on monarchE

Abemaciclib in combination with ET has been approved by the European Medicines Agency as adjuvant treatment of adult patients with HR-positive, HER2-negative, node-positive EBC at high risk of recurrence.[10] This approval is based on the results of the phase III monarchE study.[11]

The trial randomised 5,637 patients with HR-positive, HER2-negative, node-positive EBC at high risk of recurrence to receive at least five years of ET, with or without the CDK4/6i abemaciclib (150 mg orally twice a day) for two years.[11] In cohort 1 of the study, abemaciclib plus ET significantly improved iDFS (HR[95% CI]: 0.67[0.59-0.76]) and DRFS (HR[95% CI]: 0.67[0.58-0.76]) compared to ET alone (***Figure 1***). The sustained abemaciclib benefit translated to a continuous separation of the curves indicating that the benefits of abemaciclib not only persist but also increase over time, even after the treatment has ended. This carry-over effect of abemaciclib underscores the long-term efficacy of this treatment in reducing the risk of cancer recurrence in patients with high-risk EBC.

SUMMARY

The carry-over effect observed with abemaciclib in EBC treatment highlights its sustained and increasing benefit in reducing disease recurrence, supporting its use in patients with high-risk, HR-positive, HER2-negative, node-positive EBC. Treatment duration, treatment adherence and treatment choice may influence the carry-over effect. Providing patient-tailored treatment may reduce the risk of disease recurrence.

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MINIMAL INFORMATIONS OF THE SPC 1. NAME OF THE MEDICINAL PRODUCT Verzenios 50 mg film-coated tablets Verzenios 100 mg film-coated tablets Verzenios 150 mg film-coated tablets **2. QUALITATIVE AND QUANTITATIVE COMPOSITION** Verzenios 50 mg film-coated tablets Each film-coated tablet contains 50 mg abemaciclib. *Excipients with known effect* Each film-coated tablet contains 14 mg of lactose monohydrate. Verzenios 100 mg film-coated tablets Each film-coated tablet contains 100 mg abemaciclib. *Excipients with known effect* Each film-coated tablet contains 28 mg of lactose monohydrate. Verzenios 150 mg film-coated tablets Each film-coated tablet contains 150 mg abemaciclib. *Excipients with known effect* Each film-coated tablet contains 42 mg of lactose monohydrate. For the full list of excipients, see section 6.1. **3. PHARMACEUTICAL FORM** Film-coated tablet (tablet). Verzenios 50 mg film-coated tablets Beige, oval tablet of 5.2 x 9.5 mm, debossed with "Lilly" on one side and "50" on the other. Verzenios 100 mg film-coated tablets White, oval tablet of 6.6 x 12.0 mm, debossed with "Lilly" on one side and "100" on the other. Verzenios 150 mg film-coated tablets Yellow, oval tablet of 7.5 x 13.7 mm, debossed with "Lilly" on one side and "150" on the other. **4. CLINICAL PARTICULARS 4.1 Therapeutic indications** Early breast cancer Verzenios in combination with endocrine therapy is indicated for the adjuvant treatment of adult patients with hormone receptor (HR)positive, human epidermal growth factor receptor 2 (HER2)negative, nodepositive early breast cancer at high risk of recurrence (see section 5.1). In pre or perimenopausal women, aromatase inhibitor endocrine therapy should be combined with a luteinising hormonereleasing hormone (LHRH) agonist. Advanced or metastatic breast cancer Verzenios is indicated for the treatment of women with hormone receptor (HR)positive, human epidermal growth factor receptor 2 (HER2)negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy. In pre- or perimenopausal women, the endocrine therapy should be combined with a LHRH agonist. **4.2 Posology and method of administration** Verzenios therapy should be initiated and supervised by physicians experienced in the use of anticancer therapies. Posology The recommended dose of abemaciclib is 150 mg twice daily when used in combination with endocrine therapy. Please refer to the summary of product characteristics of the endocrine therapy combination partner for the recommended posology. *Duration of treatment Early breast cancer* Verzenios should be taken continuously for two years, or until disease recurrence or unacceptable toxicity occurs. *Advanced or metastatic breast cancer* Verzenios should be taken continuously as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs. If a patient vomits or misses a dose of Verzenios, the patient should be instructed to take the next dose at its scheduled time; an additional dose should not be taken. *Dose adjustments* Management of some adverse reactions may require dose interruption and/or dose reduction as shown in Tables 1-7. **Table 1. Dose adjustment recommendations for adverse reactions** Recommended dose **Verzenios dose combination therapy** 150 mg twice daily First dose adjustment **Verzenios dose combination therapy** 100 mg twice daily Second dose adjustment **Verzenios dose combination therapy** 50 mg twice daily **Table 2. Management recommendations for haematologic toxicities** Complete blood counts should be monitored prior to the start of Verzenios therapy, every two weeks for the first two months, monthly for the next two months, and as clinically indicated. Before treatment initiation, absolute neutrophil counts (ANC) ≥ 1 500 / mm^3, platelets ≥ 1 00 000 / mm^3, and haemoglobin ≥ 8 g/dL are recommended. **Toxicity[a,b]** Grade 1 or 2 **Management recommendations** No dose adjustment required. **Toxicity[a,b]** Grade 3 **Management recommendations** Suspend dose until toxicity resolves to Grade 2 or less. Dose reduction is not required. **Toxicity[a, b]** Grade 3, recurrent; or Grade 4 **Management recommendations** Suspend dose until toxicity resolves to Grade 2 or less. Resume at next lower dose. **Toxicity[a,b]** Patient requires administration of blood cell growth factors **Management recommendations** Suspend abemaciclib dose for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to Grade 2 or less. Resume at next lower dose unless the dose was already reduced for the toxicity that led to the use of the growth factor. **[a]NCI Common Terminology Criteria for Adverse Events (CTCAE) [b]ANC: Grade 1: ANC < LLN – 1 500 / mm^3; Grade 2: ANC 1 000 - < 1 500 / mm^3; Grade 3: ANC 500 - < 1 000 / mm^3; Grade 4: ANC < 500 / mm^3 LLN = lower limit of normal Table 3. Management recommendations for diarrhoea** Treatment with antidiarrhoeal agents, such as loperamide, should be started at the first sign of loose stools. **Toxicity[a]** Grade 1 **Management recommendations** No dose adjustment required. **Toxicity[a]** Grade 2 **Management recommendations** If toxicity does not resolve within 24 hours to Grade 1 or less, suspend dose until resolution. Dose reduction is not required. **Toxicity[a]** Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures **Management recommendations** Suspend dose until toxicity resolves to Grade 1 or less. Resume at next lower dose. **Toxicity[a]** Grade 3 or 4 or requires hospitalisation **Management recommendations** Suspend dose until toxicity resolves to Grade 1 or less. Resume at next lower dose. [a]NCI CTCAE **Table 4. Management recommendations for increased aminotransferases** Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) should be monitored prior to the start of Verzenios therapy, every two weeks for the first two months, monthly for the next two months, and as clinically indicated. **Toxicity[a]** Grade 1 (> ULN - 3.0 x ULN) Grade 2 (> 3.0 - 5.0 x ULN) **Management recommendations** No dose adjustment required. **Toxicity[a]** Persistent or Recurrent Grade 2, or Grade 3 (> 5.0 - 20.0 x ULN) **Management recommendations** Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose. **Toxicity[a]** Elevation in AST and/or ALT > 3 x ULN WITH total bilirubin > 2 x ULN, in the absence of cholestasis **Management recommendations** Discontinue abemaciclib. **Toxicity[a]** Grade 4 (> 20.0 x ULN) **Management recommendations** Discontinue abemaciclib. [a] NCI CTCAE ULN = upper limit of normal **Table 5. Management recommendations for interstitial lung disease (ILD)/pneumonitis Toxicity[a]** Grade 1 or 2 **Management recommendations** No dose adjustment required. **Toxicity[a]** Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1 **Management recommendations** Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose. **Toxicity[a]** Grade 3 or 4 **Management recommendations** Discontinue abemaciclib. [a]NCI CTCAE **Table 6. Management recommendations for venous thromboembolic events (VTEs) Toxicity[a] Early breast cancer** All Grades (1, 2, 3, or 4) **Management recommendations** Suspend dose and treat as clinically indicated. Abemaciclib may be resumed when the patient is clinically stable. **Toxicity[a] Advanced or metastatic breast cancer** Grade 1 or 2 **Management recommendations** No dose modification is required. Grade 3 or 4 **Management recommendations** Suspend dose and treat as clinically indicated. Abemaciclib may be resumed when the patient is clinically stable. [a]NCI CTCAE **Table 7. Management recommendations for non-haematologic toxicities (excluding diarrhoea, increased aminotransferases, and ILD/pneumonitis and VTEs) Toxicity[a]** Grade 1 or 2 **Management recommendations** No dose adjustment required. **Toxicity[a]** Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures to baseline or Grade 1 within 7 days **Management recommendations** Suspend dose until toxicity resolves to Grade 1 or less. Resume at next lower dose. **Toxicity[a]** Grade 3 or 4 **Management recommendations** Suspend dose until toxicity resolves to Grade 1 or less. Resume at next lower dose. [a]NCI CTCAE *CYP3A4 inhibitors* Concomitant use of strong CYP3A4 inhibitors should be avoided. If strong CYP3A4 inhibitors cannot be avoided, the abemaciclib dose should be reduced to 100 mg twice daily. In patients who have had their dose reduced to 100 mg abemaciclib twice daily and in whom coadministration of a strong CYP3A4 inhibitor cannot be avoided, the abemaciclib dose should be further reduced to 50 mg twice daily. In patients who have had their dose reduced to 50 mg abemaciclib twice daily and in whom coadministration of a strong CYP3A4 inhibitor cannot be avoided, the abemaciclib dose may be continued with close monitoring of signs of toxicity. Alternatively, the abemaciclib dose may be reduced to 50 mg once daily or discontinued. If the CYP3A4 inhibitor is discontinued, the abemaciclib dose should be increased to the dose used prior to the initiation of the CYP3A4 inhibitor (after 3 to 5 half-lives of the CYP3A4 inhibitor). *Special populations Elderly* No dose adjustment is required based on age (see section 5.2). *Renal impairment* No dose adjustments are necessary in patients with mild or moderate renal impairment. There are no data regarding abemaciclib administration in patients with severe renal impairment, end stage renal disease, or in patients on dialysis (see section 5.2). Abemaciclib should be administered with caution in patients with severe renal impairment, with close monitoring for signs of toxicity. *Hepatic impairment* No dose adjustments are necessary in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. In patients with severe (Child Pugh C) hepatic impairment, a decrease in dosing frequency to once daily is recommended (see section 5.2). *Paediatric population* The safety and efficacy of abemaciclib in children and adolescents aged less than 18 years has not been established. No data are available. Method of administration Verzenios is for oral use. The dose can be taken with or without food. It should not be taken with grapefruit or grapefruit juice (see section 4.5). Patients should take the doses at approximately the same times every day. The tablet should be swallowed whole (patients should not chew, crush, or split tablets before swallowing). **4.3 Contraindications** Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. **4.8 Undesirable effects** Summary of the safety profile The most commonly occurring adverse reactions are diarrhoea, infections, neutropenia, leukopenia, anaemia, fatigue, nausea, vomiting, alopecia and decreased appetite. Of the most common adverse reactions, Grade ≥ 3 events were less than 5 % with the exception of neutropenia, leukopenia, and diarrhoea. Tabulated list of adverse reactions In the following table, adverse reactions are listed in order of MedDRA body system organ class and frequency. Frequency gradings are: very common (≥1 / 10), common (≥1 / 100 to < 1 / 10), uncommon (≥1 / 1 000 to < 1 / 100), rare (≥1 / 10 000 to < 1 / 1 000), very rare (< 1 / 10 000), and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. **Table 8. Adverse reactions reported in the phase 3 studies of abemaciclib in combination with endocrine therapy[a] (N = 3 559) and during post-marketing experience System organ class** *Infections and infestations* **Very common** Infections[b] *Blood and lymphatic system disorders* **Very common** Neutropenia Leukopenia Anaemia Thrombocytopenia Lymphopenia[h] **Uncommon** Febrile neutropenia[e] *Metabolism and nutrition disorders* **Very common** Decreased appetite *Nervous system disorders* **Very common** Headache[f] Dysgeusia[g] Dizziness[g] *Eye disorders* **Common** Lacrimation increased **Uncommon** Photopsia *Vascular disorders* **Common** Venous thromboembolism[c] *Respiratory, thoracic and mediastinal disorders* **Common** ILD/pneumonitis[d]

	Hospital price	Patient price
MBC / EBC		
Verzenios® 150 mg (56 tablets)	**€ 1984,44**	**€ 0**
Verzenios® 100 mg (56 tablets)	**€ 1984,44**	**€ 0**
Verzenios® 50 mg (56 tablets)	**€ 1984,44**	**€ 0**

Gastrointestinal disorders **Very common** Diarrhoea Vomiting Nausea Stomatitis[f] **Common** Dyspepsia[f] *Skin and subcutaneous tissue disorders* **Very common** Alopecia[g] Pruritus[g] Rash[g] **Common** Nail disorder[f] Dry skin[e] **Rare** Erythema multiforme *Musculoskeletal and connective tissue disorders* **Common** Muscular weakness [e] *General disorders and administration site conditions* **Very common** Pyrexia[e] Fatigue *Investigations* **Very common** Alanine aminotransferase increased[g] Aspartate aminotransferase increased[g] [a]Abemaciclib in combination with anastrozole, letrozole, exemestane, tamoxifen, or fulvestrant. [b]Infections include all reported preferred terms that are part of the system organ class infections and infestations. [c]Venous thromboembolic events include deep vein thrombosis (DVT), pulmonary embolism, cerebral venous sinus thrombosis, subclavian, axillary vein thrombosis, DVT inferior vena cava and pelvic venous thrombosis. [d]ILD/pneumonitis for early breast cancer (EBC) include all reported preferred terms that are part of the MedDRA SMQ interstitial lung disease. For metastatic breast cancer (mBC) preferred terms include interstitial lung disease, pneumonitis, organising pneumonia, pulmonary fibrosis and bronchiolitis obliterans. [e]Considered ADRs in the mBC setting only (MONARCH 2 and MONARCH 3). [f]Considered ADRs in the EBC setting only (monarchE). [g]Common frequency in the EBC setting (monarchE), very common in the mBC setting (MONARCH 2 and MONARCH 3). [h]Common frequency in mBC setting (MONARCH 2 and MONARCH 3), very common in the EBC setting (monarchE). Description of selected adverse reactions *Neutropenia* Neutropenia was reported frequently across studies. In the monarchE study, neutropenia was reported in 45.8 % of patients. Grade 3 or 4 decrease in neutrophil counts (based on laboratory findings) was reported in 19.1 % of patients receiving abemaciclib in combination with endocrine therapy with a median time to onset of 30 days, and median time to resolution of 16 days. Febrile neutropenia was reported in 0.3 % patients. In MONARCH 2 and MONARCH 3 studies, neutropenia was reported in 45.1 % of patients. Grade 3 or 4 decrease in neutrophil counts (based on laboratory findings) was reported in 28.2 % of patients receiving abemaciclib in combination with aromatase inhibitors or fulvestrant. The median time to onset of Grade 3 or 4 neutropenia was 29 to 33 days, and median time to resolution was 11 to 15 days. Febrile neutropenia was reported in 0.9 % patients. Dose modification is recommended for patients who develop Grade 3 or 4 neutropenia (see section 4.2). *Diarrhoea* Diarrhoea was the most commonly reported adverse reaction (see Table 8). Incidence was greatest during the first month of abemaciclib treatment and was lower subsequently. In the monarchE study, the median time to onset of the first diarrhoea event of any grade was 8 days. The median duration of diarrhoea was 7 days for Grade 2 and 5 days for Grade 3. In MONARCH 2 and MONARCH 3 studies, the median time to onset of the first diarrhoea event of any grade was approximately 6 to 8 days. The median duration of diarrhoea was 9 to 12 days for Grade 2 and 6 to 8 days for Grade 3. Diarrhoea returned to baseline or lesser grade with supportive treatment such as loperamide and/or dose adjustment (see section 4.2). *Increased aminotransferases* In the monarchE study, ALT and AST elevations were reported frequently (12.3 % and 11.8 %, respectively) in patients receiving abemaciclib in combination with endocrine therapy. Grade 3 or 4 ALT or AST elevations (based on laboratory findings) were reported in 2.6 % and 1.6 % patients. The median time to onset of Grade 3 or 4 ALT elevation was 118 days, and median time to resolution was 14.5 days. The median time to onset of Grade 3 or 4 AST elevation was 90.5 days, and median time to resolution was 11 days. In MONARCH 2 and MONARCH 3 studies, ALT and AST elevations were reported frequently (15.1 % and 14.2 %, respectively) in patients receiving abemaciclib in combination with aromatase inhibitors or fulvestrant. Grade 3 or 4 ALT or AST elevations (based on laboratory findings) were reported in 6.1 % and 4.2 % patients. The median time to onset of Grade 3 or 4 ALT elevation was 57 to 61 days, and median time to resolution was 14 days. The median time to onset of Grade 3 or 4 AST elevation was 71 to 185 days, and median time to resolution was 13 to 15 days. Dose modification is recommended for patients who develop Grade 3 or 4 ALT or AST increase (see section 4.2). *Creatinine* Although not an adverse reaction, abemaciclib has been shown to increase serum creatinine. In the monarchE study, 99.3 % of patients had serum creatinine elevations (based on laboratory findings), and of these, 0.5 % of patients had Grade 3 or 4 elevations. In patients receiving endocrine therapy alone, 91.0 % reported an increase in serum creatinine (all laboratory grades). In MONARCH 2 and MONARCH 3 studies, 98.3 % of patients had serum creatinine elevations (based on laboratory findings), and of these, 1.9 % of patients had Grade 3 or 4 elevations. In patients receiving an aromatase inhibitor or fulvestrant alone, 78.4 % reported an increase in serum creatinine (all laboratory grades). Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters without affecting glomerular function (as measured by iohexol clearance) (see section 4.5). In clinical studies, increases in serum creatinine occurred within the first month of abemaciclib dosing, remained elevated but stable through the treatment period, were reversible upon treatment discontinuation, and were not accompanied by changes in markers of renal function, such as blood urea nitrogen (BUN), cystatin C, or calculated glomerular filtration rate based on cystatin C. 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: Belgium : Agence fédérale des médicaments et des produits de santé, www.afmps.be, Division Vigilance: Site internet: www.notifieruneffetindesirable.be, e-mail: adr@fagg-afmps.be. Luxembourg : Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé Site internet : www.guichet.lu/pharmacovigilance. **7. MARKETING AUTHORISATION HOLDER** Eli Lilly Nederland B.V., Papendorpseweg 83, 3528BJ Utrecht, The Netherlands. **8. MARKETING AUTHORISATION NUMBER(S)** EU/1/18/1307/001 EU/1/18/1307/002 EU/1/18/1307/003 EU/1/18/1307/004 EU/1/18/1307/005 EU/1/18/1307/006 EU/1/18/1307/007 EU/1/18/1307/008 EU/1/18/1307/009 EU/1/18/1307/010 EU/1/18/1307/011 EU/1/18/1307/012 EU/1/18/1307/013 EU/1/18/1307/014 EU/1/18/1307/015 EU/1/18/1307/016 EU/1/18/1307/017 EU/1/18/1307/018 EU/1/18/1307/019 EU/1/18/1307/020 EU/1/18/1307/021 **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION** Date of first authorisation: 27 September 2018 Date of latest renewal: 23 June 2023 **10. DATE OF REVISION OF THE TEXT** 4 July 2024. Detailed information on this medicinal product is available on the website of the European Medicines Agency: http://www.ema.europa.eu **METHOD OF DELIVERY** Medicinal product subject to restricted medical prescription.