אפריל 2019

רופא/ה נכבד/ה, רוקח/ת נכבד/ה,

הנדון: **Kisqali 200 mg film-coated tablets**
קיסקלי 200 מ"ג טבליות מצופות

אנו שמחים להודיע על הרחבת ההתוויה לתכשיר שבנדון אשר אושרה על ידי משרד הבריאות הישראלי.

ההתוויה המורחבת כפי שאושרה היא:

Kisqali is indicated in combination with:

- a non-steroidal aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer, as initial endocrine-based therapy; or
- fulvestrant for the treatment of men and postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine-based therapy or following disease progression on endocrine therapy.

המרכיב הפעיל:

Ribociclib 200 mg (as Ribociclib succinate 254.40 mg)

העלונים לרופא ולצרכן עודכנו בהתאם.
לתשומת לבכם, בנוסף להרחבת התוויה, העלונים כוללים שינויים נוספים לפי הפירוט שלהלן.

בעלון לרופא:
תוספת – מסומנת בקו תחתי
מחיקת טקסט – ~~קו חוצה~~
החמרות – טקסט מודגש בצהוב

4. CLINICAL PARTICULARS

Therapeutic indications 4.1

Kisqali is indicated in combination with:

- a non-steroidal aromatase inhibitor ~~is indicated~~ for the treatment of pre/perimenopausal or postmenopausal women, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer, as initial endocrine-based therapy; or

fulvestrant for the treatment of men and postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine-based therapy or following disease progression on endocrine therapy.

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4.2 Posology and method of administration

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Kisqali should be used together with 2.5 mg letrozole or another non-steroidal aromatase inhibitor or with 500 mg fulvestrant.
When Kisqali is used in combination with a non-steroidal aromatase inhibitor, the non steroidal aromatase inhibitor should be taken orally once daily continuously throughout the 28-day cycle. Please refer to the Prescribing information of the non-steroidal aromatase inhibitor for additional details.

When Kisqali is used in combination with fulvestrant, fulvestrant is administered intramuscularly on days 1, 15 and 29, and once monthly thereafter. Please refer to the Prescribing information of fulvestrant for additional details.

Treatment of pre- and perimenopausal women with the approved Kisqali combinations should also include an LHRH agonist in accordance with local clinical practice.

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Paediatric population
~~The safety and efficacy of Kisqali in children and adolescents aged below 18 years have not been established. No data are available.~~Kisqali is not indicated for use in children and adolescents**.**

4.4 Special warnings and precautions for use

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QT interval prolongation

In study E2301 (MONALEESA-7), a QTcF interval increase >60 msec from baseline was observed in 14/87 (16.1%) patients receiving Kisqali plus tamoxifen and in 18/245 (7.3%) patients receiving Kisqali plus a non-steroidal aromatase inhibitor (NSAI). Kisqali is not recommended to be used in combination with tamoxifen (see sections 4.8 and 5.1).
....
Appropriate monitoring of serum electrolytes (including potassium, calcium, phosphorus and magnesium) should be performed before initiating treatment, at the beginning of the first 6 cycles and then as clinically indicated. Any abnormality should be corrected before initiating treatment with Kisqali and during treatment with Kisqali.
.....

Women of childbearing potential

Women of childbearing potential should be advised to use an effective method of contraception while taking Kisqali and for at least 21 days after the last dose (see section 4.6).

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4.5 Interaction with other medicinal products and other forms of interaction

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Substances that may increase ribociclib plasma concentrations

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Patients should be instructed to avoid ~~pomegranates or pomegranate juice and~~ grapefruit or grapefruit juice. These are known to inhibit cytochrome CYP3A4 enzymes and may increase the exposure to ribociclib.

....

Substances that may have plasma concentrations altered by Kisqali

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~~It is currently unknown whether Kisqali may reduce the effectiveness of systemically-acting hormonal contraceptives.~~

Drug-drug interaction between ribociclib and anastrozole

Data from a clinical study in patients with breast cancer indicated no clinically relevant drug interaction between ribociclib and anastrozole following co-administration of these medicinal products.

Drug-drug interaction between ribociclib and fulvestrant

Data from a clinical study in patients with breast cancer indicated no clinically relevant effects of fulvestrant on ribociclib exposure following co-administration of these medicinal products.

Drug-drug interaction between ribociclib and tamoxifen

Data from a clinical study in patients with breast cancer indicated that tamoxifen exposure was increased approximately 2-fold following co-administration of ribociclib and tamoxifen.

Drug-drug interactions between ribociclib and oral contraceptives

Drug-drug interaction studies between ribociclib and oral contraceptives have not been conducted (see section 4.6).

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Kisqali is also not recommended to be used in combination with tamoxifen (see sections 4.1, 4.4 and 5.1).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

Pregnancy status should be verified prior to starting treatment with Kisqali.

~~Based on findings in animals, ribociclib can cause foetal harm when administered to a pregnant woman (see section 5.3).~~

Women of childbearing potential who are receiving Kisqali should use effective contraception (e.g.

double-barrier contraception) during therapy and for at least 21 days after stopping treatment with Kisqali.

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Based on findings in animals, ribociclib can cause foetal harm when administered to a pregnant woman (see section 5.3). Kisqali is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is not known if ribociclib is present in human milk. There are no data on the effects of ribociclib on the breast-fed infant or the effects of ribociclib on milk production. Ribociclib and its metabolites readily passed into the milk of lactating rats. Patients receiving Kisqali should not breast-feed for at least 21 days after the last dose.

Fertility

There are no clinical data available regarding effects of ribociclib on fertility. Based on animal studies, ribociclib may impair fertility in males of reproductive potential (see section 5.3).
~~For further information concerning pregnancy, lactation and fertility, see section 5.3.~~

4.7 Effects on ability to drive and use machines

Kisqali may have minor influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines in case they experience fatigue, dizziness or vertigo during treatment with Kisqali (see section 4.8).

4.8 Undesirable effects

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The most common ADRs and the most common grade 3/4 ADRs (reported at a frequency ≥20% and ≥2%, respectively) in the pooled dataset for which the frequency for Kisqali plus ~~letrozole~~ any combination exceeds the frequency for placebo plus any combination~~letrozole~~ were infections, neutropenia, leukopenia, headache, cough, ~~back pain,~~ nausea, fatigue, diarrhoea, vomiting, constipation, alopecia and rash, and infections, neutropenia, leukopenia, anaemia, abnormal liver function tests, lymphopenia, hypophosphataemia~~,~~ and vomiting~~, nausea, fatigue and back pain,~~ respectively.

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Table 6 Adverse drug reactions observed in the three phase III clinical ~~study~~studies

Adverse drug reaction	Frequency
Infections and infestations	
~~Urinary tract infection~~	~~Very common~~
Infections[1]	Very common
Blood and lymphatic system disorders	
Neutropenia, leukopenia, anaemia~~, lymphopenia~~ Lymphopenia, ~~T~~thrombocytopenia, febrile neutropenia	Very common Common
Metabolism and nutrition disorders	
Decreased appetite Hypocalcaemia, hypokalaemia, hypophosphataemia	Very common Common
Nervous system disorders	
Headache, ~~insomnia~~dizziness	Very common
Vertigo	Common
Eye disorders	
Lacrimation increased, dry eye	Common
Cardiac disorders	
Syncope	Common
Respiratory, thoracic and mediastinal disorders	
Dyspnoea, cough ~~Epistaxis~~	Very common ~~Common~~
Gastrointestinal disorders	
Nausea, diarrhoea, vomiting, constipation, stomatitis, abdominal pain[2] Dysgeusia, dyspepsia	Very common Common
Hepatobiliary disorders	
~~Hepatotoxicity~~[1]Hepatotoxicity[3]	Common
Skin and subcutaneous tissue disorders	
Alopecia, ~~rash~~[2]rash[4], pruritus Erythema, dry skin, vitiligo	Very common Common
Musculoskeletal and connective tissue disorders	
Back pain	Very common

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General disorders and administration site conditions	
Fatigue, peripheral oedema, asthenia, pyrexia	Very common
Dry mouth, oropharyngeal pain	Common
Investigations	
Abnormal liver function ~~tests[3]~~tests[5] Blood creatinine increased, ~~weight decreased,~~ electrocardiogram QT prolonged	Very common Common
[1] Infections: urinary tract infections, respiratory tract infections, gastroenteritis, sepsis (<1%). [2] Abdominal pain: abdominal pain, abdominal pain upper. [3] Hepatotoxicity: hepatocellular injury, drug-induced liver injury (<1%), hepatotoxicity, hepatic failure ~~(single non-fatal case),~~ autoimmune hepatitis (single case). [4] Rash: rash, rash maculopapular, rash pruritic. [5] Abnormal liver function tests: ALT increased, AST increased, blood bilirubin increased.	

Hepatobiliary toxicity

In the phase III clinical ~~study~~studies, hepatobiliary toxicity events occurred in a higher proportion of patients in the ~~ribociclib~~ Kisqali plus ~~letrozole~~ any combination arms compared with the placebo plus any combination~~letrozole~~ arms (~~24.0~~23.2% versus ~~13.6~~16.5%, respectively), with more grade 3/4 adverse events reported in the patients treated with ~~ribociclib~~ Kisqali plus any combination~~letrozole~~ (11.4% versus ~~3.6~~5.4%, respectively). Increases in transaminases were observed. Grade 3 or 4 increases in ALT (~~10.2~~9.7% versus ~~1.2~~1.5%) and AST (~~6.9~~6.7% versus ~~1.5~~2.1%) were reported in the ~~ribociclib~~ Kisqali and placebo arms, respectively. Concurrent elevations in ALT or AST greater than three times the upper limit of normal and total bilirubin greater than two times the upper limit of normal, with normal alkaline phosphatase, in the absence of cholestasis occurred in 6 patients (4 patients in Study A2301 [MONALEESA-2], whose levels recovered to normal within 154 days and 2 patients in Study F2301 [MONALEESA-3], whose levels recovered to normal in 121 and 532 days, respectively, after discontinuation of Kisqali). There were no such cases reported in Study E2301 (MONALEESA-7).~~4 (1.2%) patients and all patients recovered to normal levels within 154 days after treatment with Kisqali was discontinued.~~

Dose interruptions and/or adjustments due to hepato~~to~~biliary toxicity events were reported in ~~8~~10.4% of ~~ribociclib~~ Kisqali plus ~~letrozole~~ any combination treated patients, primarily due to ALT increased (~~5.7~~6.9%) and/or AST increased (~~4.5~~6.1%). Discontinuation of treatment with Kisqali plus ~~letrozole~~ any combination due to abnormal liver function tests or hepatotoxicity occurred in ~~3.0~~2.3% and 0.~~6~~4% of patients respectively (see sections 4.2 and 4.4).

In the phase III clinical ~~study~~ studies~~and a phase Ib study with ribociclib plus letrozole treatment,~~ 83.~~8~~2% (~~31~~89/~~37~~107) of grade 3 or 4 ALT or AST elevation events occurred within the first 6 months of treatment. Among the patients who had grade 3 or 4 ALT/AST elevation, the median time to onset was ~~57~~ 85 days for the ~~ribociclib~~ Kisqali plus ~~letrozole~~any combination ~~treatment group~~arms. The median time to resolution (to normalisation or grade ≤2) was ~~24~~ 22 days in the ~~ribociclib~~ Kisqali plus ~~letrozole~~ any combination arms~~group~~.

QT prolongation

In study E2301 (MONALEESA-7), the observed mean QTcF increase from baseline was approximately 10 msec higher in the tamoxifen plus placebo subgroup compared with the NSAI plus placebo subgroup, suggesting that tamoxifen alone had a QTcF prolongation effect which can contribute to the QTcF values observed in the Kisqali plus tamoxifen group. In the placebo arm, a

QTcF interval increase of >60 msec from baseline occurred in 6/90 (6.7%) patients receiving tamoxifen and in no patients receiving a NSAI (see section 5.2). A QTcF interval increase of >60 msec from baseline was observed in 14/87 (16.1%) patients receiving Kisqali plus tamoxifen and in 18/245 (7.3%) patients receiving Kisqali plus a NSAI. Kisqali is not recommended to be used in combination with tamoxifen (see section 5.1).

In the phase III clinical ~~study~~ studies ~~7.5~~8.4% of patients in the ~~ribociclib~~ Kisqali plus aromatase inhibitor or fulvestrant~~letrozole~~ arms and ~~2.4~~3.2% in the placebo plus aromatase inhibitor or fulvestrant~~letrozole~~ arms had at least one event of QT interval prolongation (including ECG QT prolonged and syncope). Review of ECG data~~(average of triplicate)~~ showed 14 patients (~~0~~1.3%) had >500 msec post-baseline QTcF value, and 59 patients (~~2.7~~5.6%) had a >60 msec increase from baseline in QTcF intervals. There were no reported cases of torsade de pointes. Dose interruptions/adjustments were reported in ~~0.9~~2.3% of ~~ribociclib~~ Kisqali plus non-steroidal aromatase inhibitor or fulvestrant~~letrozole~~ treated patients due to electrocardiogram QT prolonged and syncope.

~~A~~ The ~~central~~ analysis of ECG data ~~(average of triplicate)~~ showed ~~11~~ 52 patients (~~3.3~~4.9%) and 11 patients (~~0.3~~1.4%) with at least one >480 msec post-baseline QTcF for the ~~ribociclib~~ Kisqali plus non-steroidal aromatase inhibitor or fulvestrant~~letrozole~~ arms and the placebo plus non-steroidal aromatase inhibitor or fulvestrant~~letrozole~~ arms, respectively. Amongst the patients who had QTcF prolongation >480 msec, the median time to onset was 15 days regardless of the combination and these changes were reversible with dose interruption and/or dose reduction (see sections 4.2, 4.4 and 5.2).

4.9 Overdose

There is only limited experience with ~~are no known~~ reported cases of overdosage with Kisqali. In the event of an overdose, symptoms such as nausea and vomiting may occur. In addition, haematological (e.g. neutropenia, thrombocytopenia) toxicity and possible QTc prolongation may occur. General supportive care should be initiated in all cases of overdosage as necessary.

5.1 Pharmacodynamic properties

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In vivo studies using patient-derived oestrogen receptor-positive breast cancer xenograft model combinations of ribociclib and antioestrogens (i.e. letrozole) resulted in superior tumour growth inhibition with sustained tumour regression and delayed tumour regrowth after stopping dosing compared to each substance alone. Additionally, *in vivo* antitumour activity of ribociclib in combination with fulvestrant was assessed in immune-deficient mice bearing the ZR751 ER+ human breast cancer xenografts and the combination with fulvestrant resulted in complete tumour growth inhibition.

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Clinical efficacy and safety

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Study CLEE011E2301 (MONALEESA-7)

Kisqali was evaluated in a randomised, double-blind, placebo-controlled, multicentre phase III clinical study in the treatment of pre- and perimenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer in combination with a NSAI or tamoxifen plus goserelin versus placebo in combination with a NSAI or tamoxifen plus goserelin. Patients in MONALEESA-7 had not received prior endocrine treatment in the advanced breast cancer setting.

A total of 672 patients were randomised in a 1:1 ratio to receive either Kisqali 600 mg plus NSAI/tamoxifen plus goserelin (n=335) or placebo plus NSAI/tamoxifen plus goserelin (n=337), stratified according to: the presence of liver and/or lung metastases (Yes [n=344 (51.2%)] versus No [n=328 (48.8%)]), prior chemotherapy for advanced disease (Yes [n=120 (17.9%)] versus No [n=552 (82.1%)]), and endocrine combination partner (NSAI and goserelin [n=493 (73.4%)] versus tamoxifen and goserelin [n=179 (26.6%)]). Demographics and baseline disease characteristics were balanced and comparable between study arms. Kisqali was given orally at a dose of 600 mg daily for 21 consecutive days followed by 7 days off treatment in combination with NSAI (letrozole 2.5 mg or anastrozole 1 mg) or tamoxifen (20 mg) orally once daily for 28 days, and goserelin (3.6 mg) subcutaneously every 28 days, until disease progression or unacceptable toxicity. Patients were not allowed to cross over from placebo to Kisqali during the study or after disease progression. Switching the endocrine combination partners was also not permitted.

Patients enrolled in this study had a median age of 44 years (range 25 to 58) and 27.7% of patients were younger than 40 years old. The majority of patients included were Caucasian (57.7%), Asian (29.5%) or Black (2.8%) and nearly all patients (99.0%) had a baseline ECOG performance status of 0 or 1. Prior to study entry, of these 672 patients, 14% of patients had received prior chemotherapy for metastatic disease, 32.6% of patients had received chemotherapy in the adjuvant and 18.0% in the neoadjuvant setting; 39.6% had received endocrine therapy in the adjuvant setting and 0.7% in the neoadjuvant setting. In study E2301 40.2% of patients had *de novo* metastatic disease, 23.7% had bone-only disease, and 56.7% had visceral disease.

The study met the primary endpoint at the primary analysis conducted after 318 progression-free survival (PFS) events based on the investigator assessment using RECIST v1.1 criteria in the full analysis set (all randomised patients). The primary efficacy results were supported by PFS results based on blinded independent central radiological assessment. The median follow-up time at the time of primary PFS analysis was 19.2 months.

In the overall study population, the efficacy results demonstrated a statistically significant improvement in PFS in patients receiving Kisqali plus NSAI/tamoxifen plus goserelin compared to patients receiving placebo plus NSAI/tamoxifen plus goserelin (hazard ratio of 0.553, 95% CI: 0.441, 0.694, one-sided stratified log-rank test p-value 9.83×10^{-8}) with clinically meaningful treatment effect. Median PFS was 23.8 months (95% CI: 19.2, NE) for Kisqali plus NSAI/tamoxifen plus goserelin treated patients and 13.0 months (95% CI: 11.0, 16.4) for patients receiving placebo plus NSAI/tamoxifen plus goserelin.

Distribution of PFS is summarised in the Kaplan-Meier curve for PFS in Figure 2.

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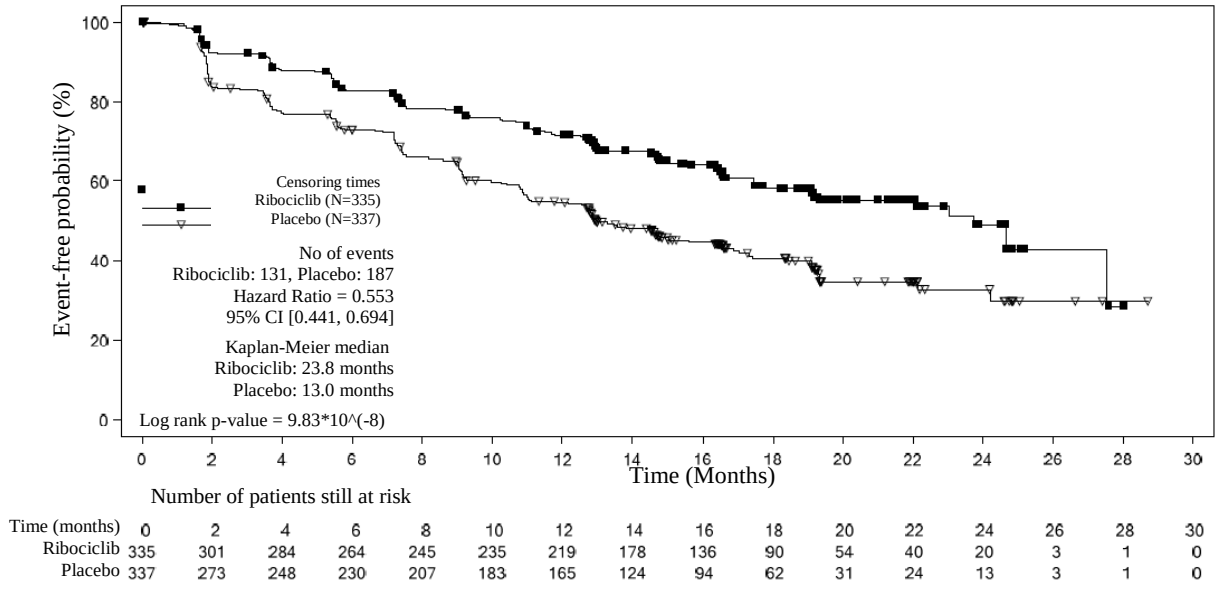
Figure 2 MONALEESA-7 - Kaplan-Meier plot of PFS in overall population based on investigator assessment



The results for PFS based on the blinded independent central radiological assessment of a randomly selected subset of approximately 40% of randomised patients were supportive of the primary efficacy results based on the investigator's assessment (hazard ratio of 0.427; 95% CI: 0.288, 0.633).

At the time of the primary PFS analysis overall survival data were not mature with 89 (13%) of deaths (HR 0. 916 [95% CI: 0.601, 1.396]).

Overall response rate (ORR) per investigator assessment based on RECIST v1.1 was higher in the Kisqali arm (40.9%; 95% CI: 35.6, 46.2) compared to the placebo arm (29.7%; 95% CI: 24.8, 34.6, p=0.00098). The observed clinical benefit rate (CBR) was higher in Kisqali arm (79.1%; 95% CI: 74.8:83.5) compared to placebo arm (69.7%; 95% CI: 64.8:74.6, p=0.002).

In the pre-specified subgroup analysis of 495 patients who had received Kisqali or placebo in combination with NSAI plus goserelin, the median PFS was 27.5 months (95% CI: 19.1, NE) in the Kisqali plus NSAI subgroup and 13.8 months (95% CI: 12.6, 17.4) in the placebo plus NSAI subgroup [HR: 0.569; 95% CI: 0.436, 0.743]. Efficacy results are summarised in Table 9 and the Kaplan-Meier curves for PFS are provided in Figure 3.

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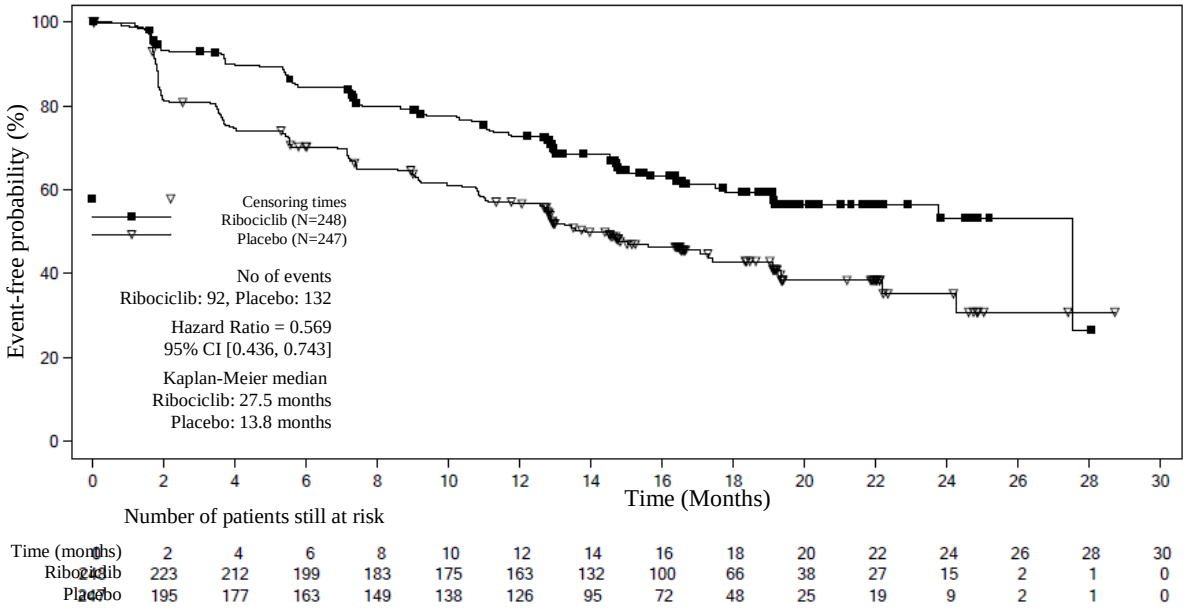
Table 9 MONALEESA-7 - Efficacy results (PFS) in patients who received NSAI

	Kisqali plus NSAI plus goserelin N=248	Placebo plus NSAI plus goserelin N=247
Progression free survival[a]		
Median PFS [months] (95% CI)	27.5 (19.1, NE)	13.8 (12.6 – 17.4)
Hazard ratio (95% CI)	0.569 (0.436, 0.743)	
CI=confidence interval; N=number of patients; NE = Not estimable. [a] – PFS based on investigator radiological assessment		

Figure 3 MONALEESA-7 – Kaplan-Meier plot of PFS based on investigator assessment in patients who received NSAI



Efficacy results for overall response rate (ORR) and clinical benefit rate (CBR) per investigator assessment based on RECIST v1.1 are provided in Table 10.

Table 10 MONALEESA-7 - Efficacy results (ORR, CBR) based on investigator assessment in patients who received NSAI

Analysis	Kisqali plus NSAI plus goserelin (%, 95% CI)	Placebo plus NSAI plus goserelin (%, 95% CI)
Full analysis set	**N=248**	**N=247**
Overall response rate (ORR)[a]	39.1 (33.0, 45.2)	29.1 (23.5, 34.8)
Clinical benefit rate (CBR)[b]	80.2 (75.3, 85.2)	67.2 (61.4, 73.1)
Patients with measurable disease	**N=192**	**N=199**
Overall response rate[a]	50.5 (43.4, 57.6)	36.2 (29.5, 42.9)
Clinical benefit rate[b]	81.8 (76.3, 87.2)	63.8 (57.1, 70.5)
[a]ORR: proportion of patients with complete response + partial response [b]CBR: proportion of patients with complete response + partial response + (stable disease or non-complete response/Non-progressive disease ≥24 weeks)		

Results in the Kisqali plus NSAI subgroup were consistent across subgroups of age, race, prior adjuvant/ neoadjuvant chemotherapy or hormonal therapies, liver and/or lung involvement and bone-only metastatic disease.

Study CLEE011F2301 (MONALEESA-3)
Kisqali was evaluated in a randomised double-blind, placebo-controlled, multicentre phase III clinical study in the treatment of men and postmenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer who had received no or only one line of prior endocrine treatment, in combination with fulvestrant versus fulvestrant alone.

A total of 726 female patients were randomised in a 2:1 ratio to receive either Kisqali 600 mg and fulvestrant (n=484) or placebo and fulvestrant (n=242), stratified according to the presence of liver and/or lung metastases (Yes [n= 351 (48.3%)] versus No [n=375 (51.7%)]) and according to prior endocrine therapy (A [n=354 (48.8%)] versus B [n=372 (51.2%)]). Demographics and baseline disease characteristics were balanced and comparable between study arms. Kisqali 600 mg or placebo were given orally daily for 21 consecutive days followed by 7 days off treatment in combination with fulvestrant 500 mg intramuscularly once daily on Days 1 and 15 in Cycle 1 and Day 1 of each subsequent 28-day cycle. Patients were not allowed to cross over from placebo to Kisqali during the study or after disease progression.

Patients enrolled in this study had a median age of 63 years (range 31 to 89). 46.7% of patients were of age 65 years and older, including 13.8% patients of age 75 years and older. The patients included were Caucasian (85.3%), Asian (8.7%) or Black (0.7%) and nearly all patients (99.7%) had an ECOG performance status of 0 or 1. First and second line patients were enrolled in this study (of whom 19.1% had *de novo* metastatic disease). Prior to study entry 42.7% of patients had received chemotherapy in the adjuvant and 13.1% in the neoadjuvant setting, while 58.5% had received endocrine therapy in the adjuvant and 1.4% in the neoadjuvant setting and 21% had received prior endocrine therapy in the advanced breast cancer setting. In study F2301 21.2% had bone-only disease and 60.5% had visceral disease.

The study met the primary endpoint at the primary analysis conducted after 361 progression-free

survival (PFS) events based on the investigator assessment and using RECIST v1.1 criteria in the full analysis set (all randomised patients). The primary efficacy results were supported by PFS results based on blinded independent central radiological assessment. The median follow-up time at the time of primary PFS analysis was 20.4 months.

The primary efficacy results demonstrated a statistically significant improvement in PFS in patients receiving Kisqali plus fulvestrant compared to patients receiving placebo plus fulvestrant in the full analysis set (hazard ratio of 0.593, 95% CI: 0.480, 0.732, one-sided stratified log-rank test p-value $4.1x10^{-7}$), with an estimated 41% reduction in relative risk of progression or death in favour of the Kisqali plus fulvestrant arm.

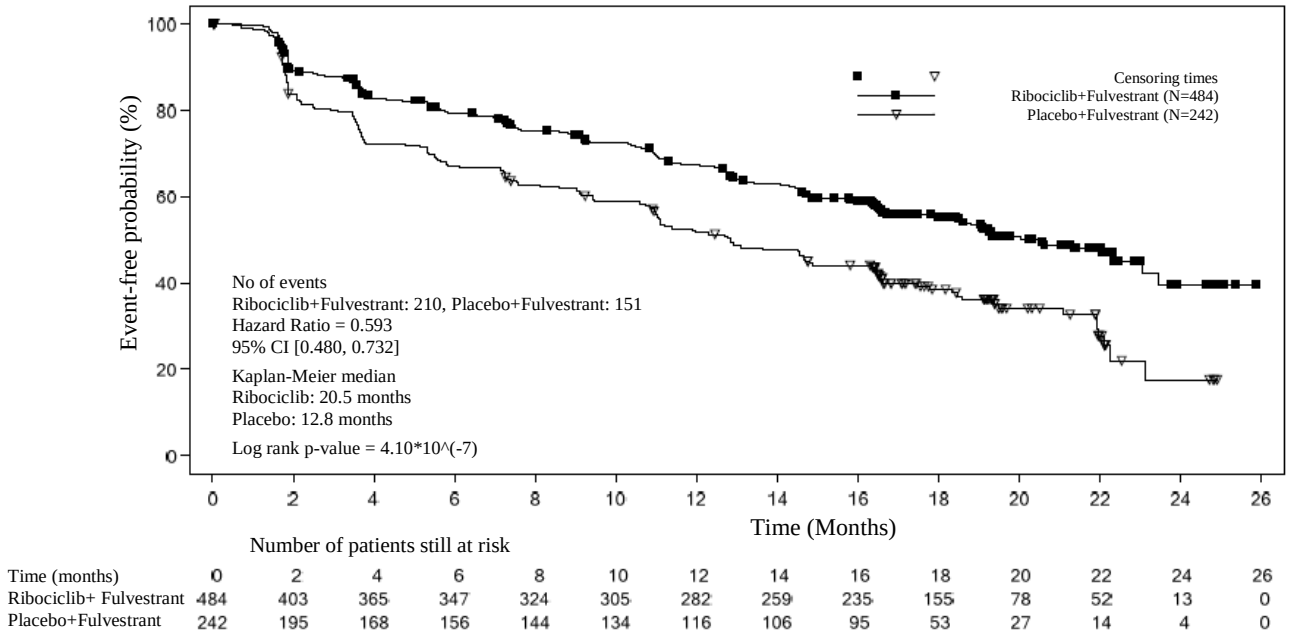
Median PFS was 20.5 months (95% CI: 18.5, 23.5) for Kisqali plus fulvestrant treated patients and 12.8 months (95% CI: 10.9, 16.3) for patients receiving placebo plus fulvestrant.

Distribution of PFS is summarised in Table 11 and in the Kaplan-Meier curve for PFS in Figure 4.

Table 11 MONALEESA-3 - Efficacy results (PFS) based on investigator radiological assessment

	Kisqali plus fulvestrant N=484	**Placebo plus fulvestrant N=242**
Progression free survival		
Median PFS [months] (95% CI)	20.5 (18.5 – 23.5)	12.8 (10.9 – 16.3)
Hazard ratio (95% CI)	0.593 (0.480 to 0.732)	
p-value[a]	0.0000410	
CI=confidence interval; N=number of patients; NE = Not estimable. [a] p-value is obtained from the one-sided stratified log-rank test.		

Figure 4 MONALEESA-3 – Kaplan-Meier plot of PFS based on investigator assessment



Number of patients still at risk

Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26
Ribociclib+ Fulvestrant	484	403	365	347	324	305	282	259	235	155	78	52	13	0
Placebo+Fulvestrant	242	195	168	156	144	134	116	106	95	53	27	14	4	0

The results for PFS based on the blinded independent central radiological assessment of a randomly selected subset of approximately 40% of randomised patients were supportive of the primary efficacy results based on the investigator's assessment (hazard ratio of 0.492; 95% CI: 0.345, 0.703).

At the time of the primary PFS analysis, overall survival data were not mature with 120 (16.5%) deaths (HR 0.670; [95%CI: 0.465, 0.964)].

Efficacy results for overall response rate (ORR) and clinical benefit rate (CBR) per investigator assessment based on RECIST v1.1 are provided in Table 12.

Table 12 MONALEESA-3 - Efficacy results (ORR, CBR) based on investigator assessment

Analysis	**Kisqali plus fulvestrant (%, 95% CI)**	**Placebo plus fulvestrant (%, 95% CI)**
Full analysis set	**N=484**	**N=242**
Overall response rate (ORR)[a]	32.4 (28.3, 36.6)	21.5 (16.3, 26.7)
Clinical benefit rate (CBR)[b]	70.2 (66.2, 74.3)	62.8 (56.7, 68.9)
Patients with measurable disease	**N=379**	**N=181**
Overall response rate[a]	40.9 (35.9, 45.8)	28.7 (22.1, 35.3)
Clinical benefit rate[b]	69.4 (64.8, 74.0).	59.7 (52.5, 66.8)
[a]ORR: proportion of patients with complete response + partial response [b]CBR: proportion of patients with complete response + partial response + (stable disease or non-complete response/Non-progressive disease ≥24 weeks)		

In the subgroup of patients who were treatment-naive in the metastatic/advanced disease setting, the hazard ratio was of 0.577 (95% CI: 0.415, 0.802), with a median PFS not reached in the Kisqali arm and 18.3 months (95% CI: 14.8, 23.1) in the placebo arm.

In the subgroup of patients who had received up to one line of treatment for metastatic/advanced disease, the hazard ratio was of 0.565 (95% CI: 0.428, 0.744), with a median PFS of 14.6 months (95% CI: 12.5, 18.5) and 9.1 months (95% CI: 6.1, 11.1) in the Kisqali and placebo arms, respectively. Within this subgroup, the hazard ratio for the second line patients who had received prior endocrine therapy in the advanced breast cancer setting was 0.539 (95% CI: 0.333, 0.873), with a median PFS of 18.8 months (95% CI: 12.5, NE) and 11.4 months (95% CI: 3.7, 16.3) in the Kisqali and placebo arms, respectively.

Hazard ratios based on pre-specified subgroup analysis of the patients treated with Kisqali plus fulvestrant showed consistent benefit across different subgroups including age, prior treatment (early or advanced), prior adjuvant/neoadjuvant chemotherapy or hormonal therapies, liver and/or lung involvement and bone-only metastatic disease.

Elderly patients
Of all patients who received Kisqali in studies MONALEESA-2 and MONALEESA-3, representative proportions of patients were ≥65 years and ≥75 years of age (see section 5.1). No overall differences in safety or effectiveness of Kisqali were observed between these patients and younger patients (see section 4.2).

5.3 Preclinical safety data

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Reproductive toxicity/Fertility

Ribociclib showed foetotoxicity and teratogenicity at doses which did not show maternal toxicity in the rats or rabbits. Following prenatal exposure, increased incidences of post-implantation loss and reduced foetal weights were observed in rats and ribociclib was teratogenic in rabbits at exposures lower than or 1.5 times the exposure in humans, respectively, at the highest recommended dose of 600 mg/day based on AUC.

....

~~Ribociclib has not been evaluated in fertility studies~~. In a fertility study in female rats, ribociclib did not affect reproductive function, fertility or early embryonic development at any dose up to 300 mg/kg/day (which is likely at an exposure lower than or equal to patients' clinical exposure at the highest recommended dose of 600 mg/day based on AUC).

Ribociclib has not been evaluated in male fertility studies. However, atrophic changes in testes were reported ~~chronic toxicity studies~~ in rat~~s~~ and dog~~s~~ toxicity studies at exposures that were less than or equal to human exposure at the highest recommended daily dose of 600 mg/day based on AUC ~~revealed atrophic changes of the tests after histopathological evaluation~~. These effects can be linked to a direct anti-proliferative effects on the testicular germ cells resulting in atrophy of the seminiferous tubules.

.....

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בעלון לצרכן:
תוספת – מסומנת בקו תחתי
מחיקת טקסט – ~~קו חוצה~~
החמרות – טקסט מודגש בצהוב

1. למה מיועדת התרופה?

קיסקלי מיועדת ~~משמשת~~ לטיפול בשילוב עם:

- מעכב ארומטאז לא סטרואידלי ~~לטיפול~~ בנשים לפני גיל המעבר, בגיל המעבר או לאחר גיל המעבר, עם סרטן שד מקומי מתקדם או גרורתי, החיוביות ל-HR, ושליליות ל-HER2 ~~בשילוב עם מעכב ארומטאז לא סטרואידלי~~ , כטיפול אנדוקריני ראשוני.
- פולווסטרנט בגברים ובנשים לאחר גיל המעבר עם סרטן שד מתקדם או גרורתי החיוביים ל-HR, ושליליים ל-HER2 כטיפול אנדוקריני ראשוני או לאחר התקדמות המחלה עם טיפול אנדוקריני.

2. לפני השימוש בתרופה
.....

! ילדים ומתבגרים
~~אין להשתמש ב~~קיסקלי אינו מיועד לטיפול בילדים ומתבגרים מתחת לגיל 18. ~~התכשיר מיועד לנשים לאחר גיל המעבר בלבד.~~

! אינטראקציות/תגובות בין תרופתיות

לפני שאת~~ה~~ מתחיל~~ה~~ ליטול קיסקלי, ספר~~י~~ לרופא או לרוקח שלך אם את~~ה~~ לוקח~~ת~~, אם לקחת לאחרונה או אם את~~ה~~ עשוי~~ה~~ לקחת תרופות אחרות כולל תרופות ללא מרשם ותוספי תזונה, מאחר והן יכולות להשפיע על אופן ההשפעה של קיסקלי. במיוחד אם את~~ה~~ לוקח~~ת~~:

- טמוקסיפן, תרופה נוספת לטיפול בסרטן השד.
.....
- אנטיביוטיקות, כגון קלאריתרומיצין, טליתרומיצין, מוקסיפלוקסאצין, ~~ו~~ריפמפיצין, ציפרופלוקסצין, לבופלוקסצין ואזיתרומיצין.
.....

קיסקלי עלולה להעלות או להוריד את הרמות בדם של תרופות אחרות. במיוחד:
טמוקסיפן, תרופה נוספת המשמשת לטיפול בסרטן השד

! שימוש בתרופה ומזון
אין לאכול אשכוליות ~~או רימונים~~ או לשתות מיץ אשכולית ~~או מיץ רימונים~~ במהלך הטיפול בקיסקלי. אלה עלולים לשנות את אופן הפירוק של קיסקלי בגופך ולהעלות את הכמות של קיסקלי בזרם הדם שלך.

! הריון והנקה

~~עלייך ליטול קיסקלי רק אם עברת את גיל המעבר.~~ אם את בהריון או מניקה, חושבת שאת יכולה להיות בהריון או מתכננת להרות, היוועצי ברופא שלך לפני נטילת תרופה זו.
הרופא שלך ידון איתך על הסיכונים האפשריים בנטילת קיסקלי במהלך ההריון.

הריון ונשים שיש להן אפשרות להיכנס להריון
אין להשתמש בקיסקלי במהלך ההריון מאחר והיא עלולה לפגוע בעובר. אם את אישה בגיל הפוריות עלייך לעבור בדיקת הריון שלילית לפני התחלת הטיפול עם קיסקלי. עלייך ~~יש~~ להשתמש באמצעי מניעה יעיל~~ים~~ (למשל: אמצעי מניעה כפול כגון קונדום ודיאפרגמה) בזמן נטילת קיסקלי ולפחות 21 ימים לאחר המנה האחרונה. שאלי את הרופא על אפשרויות לאמצעי מניעה יעיל.
~~הרופא שלך יכול לבקש בדיקת הריון שלילית לפני התחלת הטיפול בקיסקלי.~~

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הנקה
אין להניק בזמן נטילת קיסקלי ולפחות 21 ימים לאחר המנה האחרונה.

! נהיגה ושימוש במכונות
טיפול בקיסקלי עלול לגרום לעייפות, סחרחורת או לתחושת סיבוב. לכן, ישעלייך להיות זהירה בזמן נהיגה או שימוש במכונות במהלך הטיפול בקיסקלי
.....

4. תופעות לוואי
.....

- זיהום חמור עם קצב לב מוגבר, קוצר נשימה או נשימה מהירה, חום וצמרמורות (אלה עשויים להיות סימנים של אלח דם - שהוא זיהום במערכת הדם אשר עלול להיות מסכן חיים). אינו שכיחות (מופיעות עד 1 מתוך 100 אנשים).

.....

תופעות לוואי אפשריות נוספות

שכיחות מאוד *(מופיעות ביותר מ- 1 מתוך 10 אנשים~~מטופלות~~)*

- .....
- כאב גרון, נזלת, חום (סימנים לזיהום בדרכי הנשימה)
- השתנה כואבת ותכופה (סימנים לזיהום~~דלקת~~ בדרכי השתן)
- ~~קושי להירדם~~סחרחורת או תחושת סחרור
- שיעול

שכיחות *(מופיעות עד 1 מתוך 10 אנשים~~מטופלות~~)*

- כאב בטן, בחילה, הקאה ושלשול {סימנים של דלקת קיבה ומעי (גסטרואנטריטיס), שהיא זיהום במערכת העיכול}
- ~~דימום מהאף~~
- ~~ירידה במשקל~~
- ....
- תחושת סיבוב (ורטיגו)
- ערך יבש
- אובדן צבע העור בצורת כתמים (ויטיליגו)
- פה יבש
- כאב גרון (כאב בלוע)

.....

לשם הפשטות ולהקלת הקריאה, עלון זה נוסח בלשון זכר. על אף זאת, בחלק מההתוויות המאושרות התרופה מיועדת לנשים בלבד.

בנוסף למפורט לעיל, העלונים כוללים שינויים נוספים שהינם עריכתיים.

העלונים לרופא ולצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות ,וניתן לקבלם מודפסים על-ידי פניה לבעל הרישום.

בברכה,
לנה גיטלין
רוקחת ממונה

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