מרץ 2021

רופא/ה נכבד/ה

רוקח/ת נכבד/ה שלום רב,

Faslodex® 250 mg/5 ml : פרסום עדכון בעלוני התכשיר

הרכב:

One pre-filled syringe contains 250 mg fulvestrant in 5 ml solution.

התוויה:

Monotherapy

Faslodex is indicated for the treatment of estrogen receptor positive, locally advanced or metastatic breast cancer in postmenopausal women:

- Not previously treated with endocrine therapy, or
- With disease relapse on or after adjuvant endocrine therapy; or
- disease progression on endocrine therapy

Combination Therapy with Palbociclib

Faslodex is indicated for the treatment of HR-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with palbociclib in women with disease progression after endocrine therapy.

חברת אסטרהזניקה ישראל מבקשת להודיע על עדכון עלון בהתאם להוראות משרד הבריאות בתאריך **מרץ 2021.**

העדכונים המהותיים בעלון לרופא הינם:

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One pre-filled syringe contains 250 mg fulvestrant in 5 ml solution.

Excipients with known effect (per 5 ml)

Ethanol (96%. 500mg)

Benzyl alcohol (500 mg)

Benzyl benzoate (750 mg)

4.4 Special warnings and precautions for use

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Ethanol

Faslodex contains 10% w/v ethanol (alcohol) as an excipient, i.e. up to 500 mg per injection, equivalent to 10 ml beer or 4 ml wine. This may be harmful for those suffering from alcoholism and should be taken into account in high risk groups such as patients with liver disease and epilepsy.

Benzyl alcohol

Faslodex contains benzyl alcohol as an excipient which may cause allergic reactions.

4.8 Undesirable effects

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Summary of the safety profile

Combination therapy

Combination Therapy with Palbociclib (PALOMA-3)

The safety of FASLODEX 500 mg plus palbociclib 125 mg/day versus FASLODEX plus placebo was evaluated in PALOMA-3. The data described below reflect exposure to FASLODEX plus palbociclib in 345 out of 517 patients with HR-positive, HER2-negative advanced or metastatic breast cancer who received at least 1 dose of treatment in PALOMA-3. The median duration of treatment for FASLODEX plus palbociclib was 10.8 months while the median duration of treatment for FASLODEX plus placebo arm was 4.8 months.

No dose reduction was allowed for FASLODEX in PALOMA-3. Dose reductions of palbociclib due to an adverse reaction of any grade occurred in 36% of patients receiving FASLODEX plus palbociclib.

Permanent discontinuation associated with an adverse reaction occurred in 19 of 345 (6%) patients receiving FASLODEX plus palbociclib, and in 6 of 172 (3%) patients receiving FASLODEX plus placebo. Adverse reactions leading to discontinuation for those patients receiving FASLODEX plus palbociclib included fatigue (0.6%), infections (0.6%), and thrombocytopenia (0.6%).
The most common adverse reactions (≥10%) of any grade reported in patients in the FASLODEX plus palbociclib arm by descending frequency were neutropenia, leukopenia, infections, fatigue, nausea, anemia, stomatitis, , diarrhea, thrombocytopenia, , vomiting, alopecia, rash, decreased appetite, and pyrexia.

The most frequently reported Grade ≥3 adverse reactions (≥5%) in patients receiving FASLODEX plus palbociclib in descending frequency were neutropenia (1%), and leukopenia.
Adverse reactions (≥10%) reported in patients who received FASLODEX plus palbociclib or FASLODEX plus placebo in PALOMA-3 are listed in Table 2, and laboratory abnormalities are listed in Table 3.

Table 2: Adverse Reaction (≥10%) in PALOMA-3

Adverse Reactions	FASLODEX plus palbociclib (N=345)	FASLODEX plus placebo (N=172)

	All Grades %	Grade 3 %	Grade4 %	All Grades %	Grade 3 %	Grade 4 %
Infections and infestations						
Infections[1]	47[2]	3	1	31	3	0
Blood and lymphatic system disorders						
Neutropenia	83	55	11	4	1	0
Leukopenia	53	30	1	5	1	1
Anemia	30	4	0	13	2	0
Thrombocytopenia	23	2	1	0	0	0
Metabolism and nutrition disorders						
Decreased appetite	16	1	0	8	1	0
Gastrointestinal disorders						
Nausea	34	0	0	28	1	0
Stomatitis[3]	28	1	0	13	0	0
Diarrhea	24	0	0	19	1	0
Vomiting	19	1	0	15	1	0
Skin and subcutaneous tissue disorders						
Alopecia	18[4]	N/A	N/A	6[5]	N/A	N/A
Rash[6]	17	1	0	6	0	0
General disorders and administration site conditions						
Fatigue	41	2	0	29	1	0
Pyrexia	13	<1	0	5	0	0

Grading according to CTCAE 4.0.

CTCAE=Common Terminology Criteria for Adverse Events; N=number of patients; N/A=not applicable.

1. Infections includes all reported preferred terms (PTs) that are part of the System Organ Class Infections and infestations.

2. Most common infections (≥1%) include: nasopharyngitis, upper respiratory infection, urinary tract infection, influenza, bronchitis, rhinitis, conjunctivitis, pneumonia, sinusitis, cystitis, oral herpes, respiratory tract infection, gastroenteritis, tooth infection, pharyngitis, eye infection, herpes simplex, paronychia.

3. Stomatitis includes: aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal discomfort, oropharyngeal pain, stomatitis.

4. Grade 1 events – 17%; Grade 2 events – 1%.

5. Grade 1 events – 6%.

6. Rash includes: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, toxic skin eruption.

Additional adverse reactions occurring at an overall incidence of <10.0% of patients receiving FASLODEX plus palbociclib in PALOMA-3 included asthenia (7.5%), aspartate aminotransferase increased (7.5%), dysgeusia (6.7%), epistaxis (6.7%), lacrimation increased (6.4%), dry skin (6.1%), alanine aminotransferase increased (5.8%), vision blurred (5.8%), dry eye (3.8%), and febrile neutropenia (0.9%).

Table 3: Laboratory Abnormalities in PALOMA-3 i

Laboratory Parameters	FASLODEX plus palbociclib (N=345)			FASLODEX plus placebo (N=172)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
WBC decreased	99	45	1	26	0	1
Neutrophils decreased	96	56	11	14	0	1
Anemia	78	3	0	40	2	0
Platelets decreased	62	2	1	10	0	0
Aspartate aminotransferase increased	43	4	0	48	4	0
Alanine aminotransferase increased	36	2	0	34	0	0

N=number of patients; WBC=white blood cells.

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

https://sideeffects.health.gov.il

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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Combination Therapy

Patients with HR-positive, HER2-negative advanced or metastatic breast cancer who have had disease progression on or after prior adjuvant or metastatic endocrine therapy.

FASLODEX 500 mg in Combination with Palbociclib 125 mg (PALOMA-3).

PALOMA-3 (NCT-1942135) was an international, randomized, double-blind, parallel group, multi-centers study of FASLODEX plus palbociclib versus FASLODEX plus placebo conducted in women with HR-positive, HER2-negative advanced breast cancer, regardless of their menopausal status, whose disease progressed on or after prior endocrine therapy.

A total of 521 pre/postmenopausal women were randomized 2:1 to FASLODEX plus palbociclib or FASLODEX plus placebo and stratified by documented sensitivity to prior hormonal therapy, menopausal status at study entry (pre/peri versus postmenopausal), and presence of visceral metastases. Palbociclib was given orally at a dose of 125 mg daily for 21 consecutive days followed by 7 days off treatment. Fulvestrant 500 mg was administered as two 5 mL injections each containing fulvestrant 250 mg/5 mL, one in each buttock, on Days 1, 15, 29, and every 28 (+/- 3) days thereafter. Pre/perimenopausal women were enrolled in the study and received the LHRH agonist goserelin for at least 4 weeks prior to and for the duration of PALOMA-3.

Patients continued to receive assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first. The major efficacy outcome of the study was investigator-assessed PFS evaluated according to RECIST v 1.1.

Patients enrolled in this study had a median age of 57 years (range 29 to 88). The majority of patients on study were White (74%), all patients had an ECOG PS of 0 or 1, and 80% were postmenopausal. All patients had received prior systemic therapy and 75% of patients had received a previous chemotherapy regimen. Twenty-five percent of patients had received no prior therapy in the metastatic disease setting, 60% had visceral metastases, and 23% had bone only disease.

The results from the investigator-assessed PFS and final OS data from the PALOMA-3 are summarized in Table 6

The relevant Kaplan-Meier plots are shown in Figures 2 and 3, respectively. Consistent PFS results were observed across patient subgroups of disease site, sensitivity to prior hormonal therapy, and menopausal status. After a median follow-up time of 45 months, the final OS results were not statistically significant.

Table 6: Efficacy Results in PALOMA-3 – (Investigator Assessment, ITT Population)

	FASLODEX plus palbociclib	FASLODEX plus placebo
Progression-Free Survival for ITT	**(N=347)**	**(N=174)**
Number of PFS Events (%)	145 (41.8%)	114 (65.5%)
Median PFS (months) (95% CI)	9.5 (9.2-11.0)	4.6 (3.5-5.6)
Hazard Ratio (95% CI) and p-value	0.461 (0.360-0.591) p <0.0001	
Objective Response for Patients with Measurable Disease	**N=267**	**N=174**
Objective response rate[1] (%, 95% CI)	24.6 (19.6-30.2)	10.9 (6.2-17.3)
Overall Survival for ITT population	**N=347**	**N=174**
Number of OS events (%)	201 (57.9)	109 (62.6)
Median OS (months) (95% CI)	34.9 (28.8, 40.0)	28.0 (23.6, 34.6)
Hazard Ratio (95% CI) and p-value	0.814 (0.644, 1.029), p=0.0857[2,3]	

N=number of patients; PFS=progression-free survival; CI=confidence interval; ITT=Intent-to-Treat; OS=overall survival.

1. Responses are based on confirmed responses.

2. Not statistically significant at the pre-specified 2-sided alpha level of 0.047.

3. 2-sided p-value fromthe log-rank test stratified by the presence of visceral metastases and sensitivity to prior endocrine therapy per randomization.

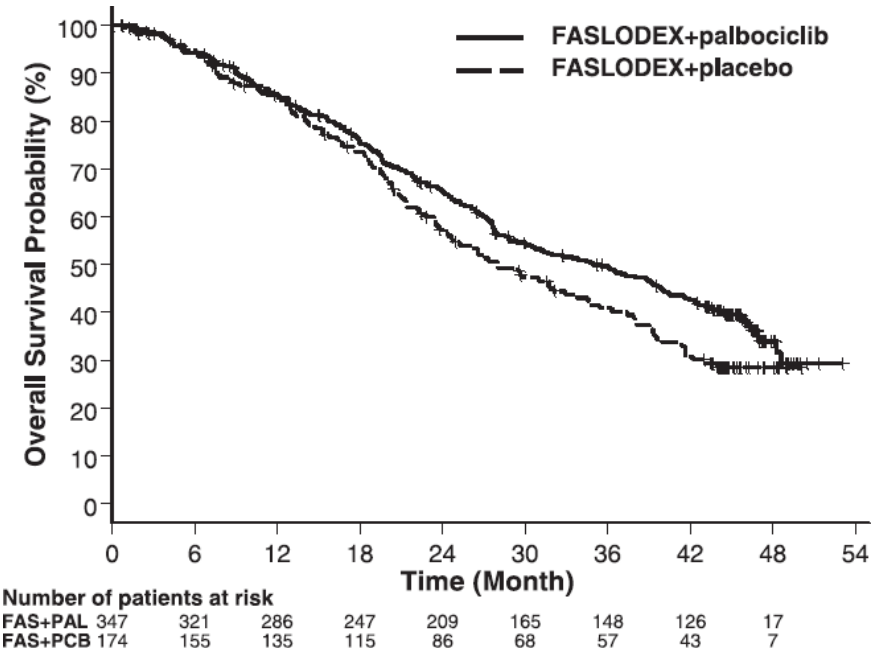
Figure 2

Kaplan-Meier Plot of Progression-Free Survival (Investigator Assessment, ITT Population) – PALOMA-3

FAS=FASLODEX; PAL=palbociclib; PCB=placebo.

Figure 3

Kaplan-Meier Plot of Overall Survival (ITT Population) – PALOMA-3



FAS=FASLODEX; PAL=palbociclib; PCB=placebo

<u>העדכונים המהותיים בעלון לצרכן הינם:</u>

2. <u>לפני שימוש בתרופה</u>

מידע חשוב על חלק מהמרכיבים:

פסלודקס מכיל 10% w/v (משקל לנפח) אתנול (אלכוהול), למשל עד 500מ"ג אלכוהול במנה, שווה ערך ל- 10מ"ל בירה או ל- 4 מ"ל יין במנה. כמות זו יכולה להזיק לאלו הסובלים מהתמכרות לאלכוהול. יש לקחת זאת בחשבון באנשים בקבוצת סיכון כגון חולים עם מחלת כבד או אפילפסיה.

פסלודקס מכיל 500 מ"ג בנזיל אלכוהול לזריקה, שווה ערך ל- 100 מ"ג/מ"ל. בנזיל אלכוהול עלול להוביל לתגובות אלרגיות.

פסלודקס מכיל 750 מ"ג בנזיל בנזואט לזריקה, שווה ערך ל- 150 מ"ג/מ"ל.

4. <u>תופעות לוואי</u>

כמו בכל תרופה, השימוש בפסלודקס עלול לגרום לתופעות לוואי בחלק מהמשתמשים. אל תיבהלי למקרא רשימת תופעות הלוואי. ייתכן ולא תסבלי מאף אחת מהן.

תופעות לוואי המחייבות התייחסות מיוחדת:

ייתכן ותזדקקי לטיפול רפואי דחוף במידה ומופיעות תופעות הלוואי הבאות:

פסלודקס כטיפול בודד:

- תגובת רגישות יתר (אלרגיה), כולל התנפחות הפנים, השפתיים, הלשון ו/או הגרון. תופעות אלה עלולות להיות סימנים לתגובות אנפליקטיות
- תרומבואמבוליזם - עלייה בסיכון לקרישי דם*.
- דלקת בכבד (הפטיטיס).
- כשל בכבד.

פסלודקס בשילוב עם פלבוציקליב:

- תסחיף ריאתי

דווחי לרופא שלך או לרוקח אם מופיעות תופעות הלוואי הבאות:

תופעות לוואי נוספות:

תופעות לוואי שמופיעות לעיתים קרובות (משפיעות על עד מטופל אחד מתוך 10 מטופלים):

- כאב ראש.
- הקאה, שלשול או אובדן תיאבון*.
- דלקת בדרכי השתן.
- כאב גב*.
- תרומבואמבוליזם - עלייה בסיכון לקרישי דם*.
- עלייה ברמת הבילירובין (פיגמנט מרה המיוצר על ידי הכבד)
- ירידה ברמות הטסיות בדם (תרומבוציטופניה).
- דימום וגינלי.
- **כאבים בגב התחתון המקרינים לרגל בצד אחד, סכיאטיקה** (SCIATICA).
- חולשה פתאומית, חוסר תחושה, עקצוצים או אובדן התנועה ברגליים, במיוחד רק בצד אחד של הגוף, בעייה פתאומית ביכולת ההליכה או בשיווי משקל (peripheral neuropathy).

פסלודקס בשילוב עם פלבוציקליב

תופעות לוואי נוספות:

-
- חולשה.

<u>מקרא לעדכונים המסומנים</u>:
תוספת טקסט מהותי מסומנת בצבע אדום.
מחיקת טקסט מסומנת בקו חוצה בצבע כחול.

העלונים מפורסמים במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום.

בכבוד רב,
קארין קנבל דובסון

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