מאי 2022

רופא/ה נכבד/ה,
רוקח/ת נכבד/ה,

הנדון:
Progyluton
Tablets
Estradiol Valerate 2mg
Norgestrel 0.5mg

חברת באייר מתכבדת להודיע כי העלונים לרופא ולצרכנית עודכנו.

ההתוויות המאושרות לתכשיר:

Two phase preparation for climacteric and cycle disturbances.

בהודעה זו כלולים העידכונים המהותיים בלבד. בפירוט שלהלן מופיע ,מתוך כל פרק ששונה בעלונים, רק המידע שהתעדכן. תוספת טקסט מסומנת בקו תחתון, מחיקת טקסט מסומנת ~~בקו חוצה~~.

העדכונים בעלון לרופא:

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4.4 Special warnings and precautions for use

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Breast cancer

Randomized controlled studies and epidemiological investigations showed an enhanced risk of developing breast cancer among women who were given HRT for several years. The risk is particularly increased with a use period of more than 5 years. In a meta-analysis of epidemiological studies, the relative risk in women who used HRT for 5 or more years was 1.35 (95% CI 1.21-1.49). In individual studies, however, an increase in risk was also observed after a shorter duration of therapy (1-4 years). In general, the risk increase was higher with combined estrogen-progestin therapy than with estrogen monotherapy. Prior to the start of HRT all women must therefore undergo breast examination by a doctor once a year, and self-examinations of the breast should be performed once a month. Depending on age and the respective risk factors, a mammogram may also be indicated. The users should be informed of which breast changes they must report to their doctor. ~~Depending on the age and the respective risk factors, mammography may be indicated in addition.~~

A two large analysis of ~~51~~ epidemiological studies revealed that the risk of contracting breast cancer increases with the duration of HRT and decreases after discontinuation of HRT. The ~~relative risk~~ (RR) time to return to age-appropriate risk baseline depends on the duration of of previous ~~contracting breast cancer was 1.35 (95% confidence interval (CI) 1.21-1.49)~~ ~~among~~

~~women receiving~~ HRT ~~for.~~ If the duration of use exceeds 5 years, the risk may still be increased for 10 years or more after discontinuation.or longer.

The Women's Health Initiative (WHI) study, a large, prospective, placebo-controlled, randomized study of more than 8,000 elderly, postmenopausal women (age at the start of the study 50-79, mean age 63), showed that, in comparison to placebo under combined HRT with conjugated estrogens and medroxyprogesterone acetate (MPA) after an average administration period of 5.6 years, there was an increase in invasive breast cancer in the estrogen/progestogen group (RR 1.24 [95% CI 1.02-1.50]).~~It is not known whether there is a similar risk for other combined HRT preparations~~. For the estrogen monotherapy, on the other hand, there was no enhanced risk (RR 0.77 [95% CI 0.59-1.01]).

The Million Women Study, a nonrandomized cohort study, recruited 1,084,110 women. The average age of the women on entering the study was 55.9 years. Half of the women received HRT before and/or at the beginning of the study, the other half had never been given HRT. 9,364 cases of invasive breast cancer and 637 deaths due to breast cancer were recorded after an average observation period of 2.6 and 4.1 years, respectively. Women who were using HRT at the beginning of the study demonstrated, in comparison with the women who had never received such a therapy, a higher morbidity risk (RR 1.66 [95% CI 1.58-1.75]) and possibly, but less pronounced, a higher mortality from breast cancer (RR 1.22 [95% CI 1.00-1.48]). The highest risk was seen in the combined estrogen/progestogen therapy group (RR 2.00 [95% CI 1.88-2.12]). The relative risk was 1.30 (95% CI 1.21-1.40) for the estrogen monotherapy. The results were similar for the different estrogens and progestogens, for the various doses and administration routes and for continuous and sequential therapy. With all the types of HRT the risk increased with the duration of administration. ~~After discontinuation of therapy the risk receded (last use more than 5 years previously): RR 1.04 [95% CI 0.95-1.12]).~~

HRT increases opacity in mammographic images, and this can impair the radiological detection of breast cancer in some cases.

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Other precautionary measures

Estrogens may cause fluid retention. Patients with conditions that may worsen as a result (such as heart or kidney function disorders, asthma, epilepsy or migraine) should therefore be monitored carefully.

~~An HRT may lead to an increase in triglyceride levels, which may increase the risk of pancreatitis in patients with preexisting hypertriglyceridemia. Therefore, the triglyceride levels should be monitored in such patients.~~

No clear association has been recorded to date between the use of HRT and the development of clinical hypertension. A slight increase in blood pressure has been seen in women on HRT, but a clinically significant increase is rare. If a continually enhanced blood

pressure is ascertained under HRT, consideration should be given to the idea of discontinuing treatment.

Patients who take hypotensive medication at the same time as Progyluton should have their blood pressure checked on a regular basis.

An HRT may lead to an increase in triglyceride levels, which may increase the risk of pancreatitis in patients with preexisting hypertriglyceridemia. Therefore, the triglyceride levels should be monitored in such patients.

~~Women with liver function disorders, including hyperbilirubinemia, such as Dubin-Johnson syndrome or rotor syndrome, must be monitored carefully, and the liver parameters must be checked. If the liver values worsen, the HRT should be discontinued.~~

~~After viral hepatitis has subsided, approximately 6 months should pass before preparations such as Progyluton are administered.~~

~~Estrogens can enhance lithogenicity in the gallbladder. As a result, the risk of gallbladder diseases (particularly cholelithiasis) is increased in some women undergoing estrogen therapy.~~

Clinical studies have demonstrated an influence of HRT on peripheral insulin resistance and glucose tolerance. As a rule, however, it is not necessary to make any adjustments to antidiabetic therapy. Diabetics on HRT should have their blood sugar levels closely monitored.

Women with hepatic function disorders, including hyperbilirubinemia such as Dubin-Johnson syndrome or rotor syndrome, must be monitored carefully and the liver parameters must also be monitored. If liver values deteriorate, HRT should be discontinued.

Oestrogens may increase the lithogenicity of bile. Several epidemiological studies found a small but statistically significant increase in the risk of gallbladder diseases (especially cholelithiasis) or an increased incidence of cholecystectomy during HRT. This should be considered especially in patients with additional risk factors for cholelithiasis (e.g., obesity, hyperlipidaemia).

It is necessary for patients with a preexisting prolactinoma to be monitored closely by the doctor (this includes regular prolactin level determinations), since it has been reported that in isolated cases prolactinomas have increased in size under estrogen therapy.

Renally impaired patients or those with metabolic bone diseases accompanied by hypercalcemia should, as with any estrogen-containing preparation, only use Progyluton after a careful weighing up of the benefits and risks.

As a result of estrogen stimulation, some patients on HRT may suffer undesired side effects, such as unusually heavy bleeding. Frequent and persistent irregular bleeding is a sign of

endometrial activity and must be clarified by appropriate diagnostic means in order to rule out organic diseases.

Uterine myomas may increase in size under estrogen therapy. If this is detected, therapy should be discontinued.

Should an endometriosis be reactivated under HRT it is recommended to discontinue this therapy.

Exogenous estrogen supply leads to an increase in serum concentrations of thyroxine-binding globulin (TBG). In women with normal thyroid function, this is of no clinical relevance. Studies suggest that in patients undergoing thyroid hormone replacement therapy, the additional administration of an estrogen preparation (such as Progyluton) could lead to increased thyroxine requirements. Patients on thyroid hormone replacement therapy should therefore have their thyroid function monitored regularly (by TSH determination), especially during the first months of HRT.

On occasions, chloasma may occur, particularly in women with a history of chloasma gravidarum. Women with a predisposition for chloasma should not expose themselves to the sun or other ultraviolet radiation during HRT.

In women with hereditary angioedema, any exogenous estrogens may trigger or exacerbate the symptoms of angioedema.

The risks of HRT reported above have been described predominantly in women over the age of 50 years. No experience is available on the transferability of these data to patients with premature menopause (i.e., failure of ovarian function before 40 due to endocrine/genetic diseases, ovariectomy, malignancy therapy, etc.) until they reach normal menopausal age. In this age group, a specific benefit-risk assessment should be performed, including consideration of the etiology of premature menopause (surgical versus other causes).

Diagnosis and initiation of therapy in patients with premature menopause should preferably be performed in an appropriate center experienced in the treatment of this clinical picture.

Progyluton has no contraceptive effect. If necessary, nonhormonal contraceptive methods should be used.

Each Progyluton white coated tablet contains 46.220 mg lactose monohydrate. Each Progyluton light brown coated tablets contain 45.720mg lactose monohydrate. Each tablet contains 33.980 mg sucrose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not use this medicine.

4.8 Undesirable effects

The serious undesirable effects linked to the use of an HRT are also described in the section “Special warnings and special precautions for use” (q.v.).

The following lists the undesirable effects by organ system and frequency, observed under HRT preparations. A connection with Progyluton cannot be corroborated, nor can it be ruled out.

The frequency brackets are defined as follows: common ≥1/100 and <1/10; uncommon ≥1/1,000 and <1/100; rare ≥1/10,000 and <1/1,000); unknown (~~based predominantly on spontaneous reports from post-market surveillance, exact frequency~~ cannot be estimated from the available data)

5.2 Pharmacokinetic properties

Metabolism

~~Norgestrel is completely metabolized. The biotransformation of levonorgestrel follows the well-known steroid metabolism path, with involvement of CYP3A4. No pharmacologically active metabolites are known.~~

Levonorgestrel is extensively metabolized in the liver. The major metabolic degradation pathways are reduction of the Δ4-3-oxo group and hydroxylations at the 2α, 1β, and 16β positions, followed by conjugation. CYP3A4 is involved as the main enzyme in the oxidative metabolism of levonorgestrel. However, available in vitro data suggest that CYP-mediated biotransformation reactions may be of secondary importance in the metabolism of levonorgestrel compared with reduction and conjugation.

Pharmacologically active metabolites of levonorgestrel are unknown.

העדכונים בעלון לצרכנית:

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2) לפני השימוש בתרופה

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סרטן השד

~~במחקרים מסוימים, סרטן השד אובחן בשכיחות גבוהה יותר במידה מסוימת בנשים אשר קיבלו טיפול הורמונלי חלופי במשך מספר שנים. סיכון זה גובר עם הארכת משך הטיפול. בעת טיפול בתכשירים המכילים אסטרוגן בלבד, סיכון מוגבר זה עשוי להיות ניטרלי. אם נשים מפסיקות את הטיפול ההורמונלי החלופי הסיכון הנוסף נעלם תוך מספר שנים.~~

מספר מחקרים דיווחו על עלייה מסוימת בסיכון לסרטן השד בנשים אשר קיבלו טיפול הורמונלי חלופי במשך חמש שנים ומעלה. במחקרים מסוימים, הסיכון עלה כבר לאחר שנה עד ארבע שנים. סיכון זה גובר בעת טיפול בתכשירים המכילים שילוב של אסטרוגן ופרוגסטרון לעומת תכשירים המכילים אסטרוגן בלבד. אם נשים מפסיקות את הטיפול ההורמונלי החלופי, הסיכון הנוסף חולף בדרגה ודומה לאותן נשים אשר לא קיבלו טיפול הורמונלי חלופי. יש לציין שתוספת הסיכון עלולה להישאר עד עשר שנים לאחר הטיפול בנשים אשר קיבלו טיפול הורמונלי חלופי במשך חמש שנים ומעלה.

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~~ידעי את הרופא או הרוקח אם את סובלת ממחלות אחרות, מאלרגיות או אם את נוטלת תרופות אחרות (לרבות אלה שרכשת בעצמך!) או משתמשת בהן באופן חיצוני!~~ כמו כן, חשוב כי תיידעי את הרופא או רופא השיניים על כך שאת נוטלת פרוגילוטון אם הוא רושם לך תרופות חדשות.

העלון לרופא והעלון לצרכנית נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות:
https://data.health.gov.il/drugs/index.html#!/byDrug
ניתן לקבלם מודפסים ע"י פניה לחברת באייר ישראל, רח' החרש 36 הוד השרון, טלפון: 09-7626700.

בברכה,

באייר ישראל