הודעה על החמרה (מידע בטיחות)

תאריך: 29.10.2012

שם תכשיר באנגלית: Vagifem 10 mcg

מספר רישום: 146-89-33241-00

שם בעל הרישום: Novo Nordisk LTD

השינויים בעלון מסומנים על רקע צהוב

בעלון לרופא

פרטים על השינוי/ים המבוקש/ים		
טקסט חדש	**טקסט נוכחי**	**פרק בעלון**
Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency, see section 4.4)	**לא הופיע**	**4.3** **Contraindications**
In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among systemic oestrogen-only users varies from 2- to 12-fold compared with non-users, depending on both duration of treatment and on oestrogen dose . After stopping treatment risk remain elevated for at least 10 years.	The risk of endometrial cancer after treatment with oral unopposed oestrogens is dependent on both duration of treatment and on oestrogen dose. The dose of estradiol in Vagifem is very low .and treatment is local	**4.4** **Special warnings and precautions for use-** **Endometrial hyperplasia and carcinoma**
The excess risk becomes apparent within a few years of use but returns to baseline within a few (at most five) years after stopping treatment.		**4.4** **Special warnings and precautions for use** **Breast cancer** **-**
Ovarian cancer is much rarer than breast cancer. Long-term (at least 5-10 years) use of oestrogen-only HRT products has been associated with a slightly increased risk of ovarian cancer. Some studies including the WHI trial suggest that the long-term use of combined HRTs may confer a similar or .(slightly smaller risk (see Section 4.8 A relationship between ovarian cancer risk and low dose local vaginal oestrogen therapy is uncertain.	**לא הופיע**	**4.4** **Special warnings and precautions for use** **- Ovarian cancer**

In women with no personal history of VTE but with first degree relative with a history of thrombosis at young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening.(If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is 'severe' (e.g. antithrombin, protein S, or protein C deficiencies or a combination of defects) HRT is contraindicated.	חלקים אלה לא הופיעו	**4.4 Special warnings and precautions for use - Venous thromboembolism**
Combined oestrogen-progestagen and oestrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischaemic stroke.	In the WHI estrogen alone sub-study, a statistically significant increased risk of stroke was reported in women receiving daily conjugated oestrogens (CE 0.625 mg) compared to placebo (45 versus 33 per 10,000 women-years	**4.4 Special warnings and precautions for use -Ischaemic stroke**
Women with pre-existing hypertriglyceridaemia should be followed closely during oestrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this condition. Oestrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone (as measured by protein-bound iodine (PBI)), T4 levels (by column or by radioimmunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex-hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).	לא הופיע	**4.4 Special warnings and precautions for use other - conditions**
However, the metabolism of oestrogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz). Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Herbal preparations containing St John's Wort (Hypericum Perforatum) may induce the metabolism of oestrogens.	טקסט זה לא הופיע	**4.5 Interaction with other medicinal products and other forms of interaction**

Breast cancer risk

Risk estimates have been drawn from systemic exposure and it is not known how these apply to local treatments.

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestagen therapy for more than 5 years.
- Any increased risk in users of oestrogen-only therapy is substantially lower than that seen in users of oestrogen-progestagen combinations.
- The level of risk is dependent on the duration of use (see section 4.4).

- Results of the largest randomised placebo-controlled trial (WHI-study) and largest epidemiological study (MWS) are presented.

Million Women Study – Estimated additional risk of breast cancer after 5 years' use

Age range (years)	Incidence per 1000 never-users of HRT over a 5 year period*	Risk ratio and 95% CI #	Additional cases per 1000 HRT users over 5 years (95% CI)
		Oestrogen only HRT	
50 – 65	9 – 12	1.2	1 - 2 (0 - 3)

* Taken from baseline incidence rates in developed countries.

Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use.

Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.

US WHI studies – additional risk of breast cancer after 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95% CI	Additional cases per 1000 HRT users over 5 years (95% CI)
		CEE oestrogen-only	
50 – 79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0) *

* WHI study in women with no uterus, which did not show an increase in risk of breast cancer

‡When the analysis was restricted to women who had not used HRT prior to the study there was no increased risk apparent during the first 5 years of treatment: after 5 years the risk was higher than in non-users.

Ovarian cancer

Risk estimates have been drawn from systemic exposure and it is not known how these apply to local treatments. Long-term use of oestrogen-only and combined oestrogen-progestagen HRT has been associated with a slightly increased risk of ovarian cancer. In the Million Women Study, 5 years of HRT resulted in 1 extra case per 2500 users.

Risk of venous thromboembolism

Risk estimates have been drawn from systemic exposure and it is not known how these apply to local treatments. HRT is associated with a 1.3-3 fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HRT (see section 4.4). Results of the WHI studies are presented:

חלקים אלה לא הופיעו בעלון המאושר

4.8

Undesirable effects

WHI Studies – Additional risk of VTE over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95% CI	Additional cases per 1000 HRT users
Oral oestrogen-only*			
50-59	7	1.2 (0.6 - 2.4)	1 (-3 – 10)

* Study in women with no uterus

Risk of coronary artery disease

Risk estimates have been drawn from systemic exposure and it is not known how these apply to local treatments. The risk of coronary artery disease is slightly increased in users of combined oestrogenprogestagen HRT over the age of 60 (see section 4.4).

Risk of ischaemic stroke

Risk estimates have been drawn from systemic exposure and it is not known how these apply to local treatments. The use of oestrogen- is associated with an up to 1.5 fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT. This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age, see section 4.4.

WHI studies combined – Additional risk of ischaemic stroke * over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95% CI	Additional cases per 1000 HRT users over 5 years
50-59	8	1.3 (1.1 – 1.6)	3 (1 – 5)

* No differentiation was made between ischaemic and haemorrhagic stroke

בעלון לצרכן

פרטים על השינוי/ים המבוקש/ים		
פרק בעלון	**טקסט נוכחי**	**טקסט חדש**
2. אין להשתמש בתרופה אם:	**לא מופיע**	אם יש לך הפרעה בקרישת הדם (blood clotting disorder, למשל, חסר בחלבון C או חסר בחלבון S או חסר באנטיטרומבין).
2. אזהרות מיוחדות הנוגעות לשימוש בתרופה	**לא הופיע**	•הימצאות ציסטות (fibroids) ברחם •אם יש לך רמות שומנים גבוהות בדם (היפרטריגליצרידמיה). •אצירת נוזלים כתוצאה מבעיות לבבית או בעיות כלייתיות.

השפעת טיפול הורמונלי חלופי (HRT) על הלב ומחזור הדם: **קרישי דם בורידים (thrombosis)**	**לא הופיע**	הסיכון להיווצרות קריש דם עולה עם העלייה בגיל. במידה ואחד או יותר מהמצבים הבאים תקף לגביך, באופן כללי קיימת סבירות גבוהה יותר להיווצרות של קריש דם ורידי. עלייך ליידע את הרופא במידה ואחד מהמצבים הבאים תקף לגביך: • את סובלת מעודף משקל רב • לאחד מקרובי המשפחה שלך היה קריש שם ברגל, בריאות או באיבר אחר בגוף. • היו לך בעיות קרישת דם כלשהן שדרשו טיפול בתרופות למניעת קרישי דם (אנטי קואגולנטים) • יש לך סרטן • אינך מסוגלת ללכת במשך תקופה ארוכה עקב ניתוח, פציעה או מחלה • יש לך מחלת זאבת אדמנתית מערכתית (SLE).
4. תופעות לוואי- **השפעת טיפול הורמונלי חלופי (HRT) על הלב ומחזור הדם:** **מחלת לב**	**לא הופיע**	מחלת לב (התקף לב) אין הוכחה לכך שטיפול הורמונלי חליפי יסייע למנוע התקף לב. הסבירות לפתח מחלת לב גבוהה במעט אצל נשים מעל גיל 60 שנים המשתמשות בטיפול הורמונלי חליפי עם אסטרוגן-פרוגסטגן לעומת נשים שאינן מטופלות בטיפול הורמונלי חליפי. אין עלייה בסיכון לפתח מחלת לב בנשים שעברו כריתת רחם ומטופלות בטיפול הורמונלי חליפי המכיל אסטרוגן בלבד.
4. תופעות לוואי- **השפעת טיפול הורמונלי חלופי (HRT) על הלב ומחזור הדם:** **שבץ**	**לא הופיע**	הסיכון לשבץ הינו פי 1.5 גבוה במטופלות בטיפול הורמונלי חליפי לעומת נשים שאינן מטופלות. מספר מקרי השבץ הנוספים בשל שימוש בטיפול הורמונלי חליפי יעלה עם העלייה בגיל.
4. תופעות לוואי- **מצבים נוספים**	**לא הופיע**	מצבים נוספים טיפול הורמונלי חליפי אינו מונע אובדן זיכרון. הסיכון לאובדן זיכרון אפשרי עשוי להיות גבוה במידת מה אצל נשים שהתחילו את הטיפול ההורמונלי החליפי לאחר גיל 65 . למידע נוסף התייעצי עם הרופא המטפל.