הודעה על החמרה (מידע בטיחות)

תאריך ___06.11.2011

שם תכשיר באנגלית_NovoFem

מספר רישום__127-11-30604-00

שם בעל הרישום נובו נורדיסק בע"מ

השינויים בעלון מסומנים ברקע צהוב

עלון 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)) - Active or previous arterial thromboembolic disease (e.g, angina, myocardial infarction).		**Contrainication**
Diabetes mellitus with or without vascular involvment	Diabetes mellitus with vascular involvment	**Special warnings and precautions for use**
<u>Endometrial Hyperplasia and carcinoma</u> 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 increas in endometrial cancer risk among oestrogen-only users varies from 2 to 12 fold greater compared with non users, depending on the duration of treatment and oestrogen dose (see section 4.8). After stopping treatment, risk may remain elevated for at least 10 years. The addition of a progestagen cyclically for at least 12 days per month/28 day cycle or continuous combined oestrogen-progestagen therapy in non-hysterectomised women prevents the excess risk associated with oestrogen-only HRT. Breakthrough bleeding and spotting may occur during the first months of treatment.	The risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods (see section 4.8). The addition of a progestagen for at least 12 days per cycle in non-hysterectomised women greatly reduces this risk. Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial	

If breakthrough bleeding or spotting continues after the first months of treatment, appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.	biopsy to exclude endometrial malignancy.	
Breast Cancer The overall evidence suggests an increased risk of breast cancer in women taking combined oestrogen-progestagen and possibly also oestrogen-only HRT, that is dependent on the duration of taking HRT. The randomised placebo controlled trial, the Women`s Health Initiative study (WHI), and epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined oestrogen-progestagen for HRT that becomes apparent after about 3 years (see section 4.8). The excess risk becomes apperant within a few years of use but returns to baseline within a few (at most five) years after stopping treatment. HRT, especially oestrogen-progestagen combined treatment, increases the density of mammographic images, which may adversely affect the radiological detection of breast cancer.	Breast Cancer A randomised placebo controlled trial, the Women`s Health Initiative study (WHI), and epidemiological studies, Including the Million Women Study (MWS), have reported an increased risk of breast cancer in women taking oestrogens, oestrogen-progestagen combinations or Tibolone for HRT for several years (see section 4.8). For all HRT, an excess risk becomes apperant within a few years of use and increases with duration of intake, but returns to baseline within a few (at most five) years after stopping treatment. In the MWS, the relative risk of breast cancer with conjugated equine oestrogens (CEE) or estradiol (E2) was greater when a progestagen was added, either sequentially or continuously, and regardless of the type of progestagen. There was no evidence of a difference in risk between the different routes of administration. In the WHI study, the continuous combined conjugated equine oestrogen and	

	medroxyprogesteron acetate (CEE+MPA) products used were associated with breast cancers that were slightly larger in size and more frequently had lymph node metastases compared to placebo. HRT, especially oestrogen-progestagen combined, treatment, increases the density of mammographic images, this may adversely affect the radiological detection of breast cancer.	
Venous Thromboembolism HRT is associated with a 1.3 – to 3 fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likley in the first year of HRT than later. (see section 4.8) Patients with known thrombophilic states have an increased risk of VTE and HRT may add to this risk. HRT is therefore contraindicated in these patients (see section 4.3). Generally recognised risk factors for VTE include use of oestrogens, older age, major surgery, prolonged immobilisation, obesity (BMI>30 kg/m^2), pregnancy/ postpartum period, systemic lupus erythematosus (SLE) and cancer. There is no consensus about the possible role of varicose veins in VTE. As in all postoperative patients, prophylactic measures need to be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery, temporarily stopping HRT four to six weeks earlier, is recommended. Treatment should not be restarted until the woman is completely mobilised. In women with no personal history of VTE but with a first degree relative with a history of thrombosis at young age,	Venous Thromboembolism HRT is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. One randomised controlled trial and epidiomological studies found a two- to three-fold higher risk for users compared with nonusers. For non-users it is estimated that the number of cases of VTE that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 8 per 1000 women aged between 60-69 years. It is estimated that in healthy women who use HRT for 5 years, the number of additional cases of VTE over a 5 years period will be between 2 and 6 (best estimate =4) per 1000 women aged 50-59 years and between 5 and 15 (best estimate=9) per 1000 women aged 60-69	

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. Women already on chronic anticoagulant treatment require careful consideration of the benefit-risk of use of HRT. If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g., painful swelling of a leg, sudden pain in the chest, dyspnoea).	years. The occurrence of such an event is more likley in the first year of HRT than later. Generally recognised risk factors for VTE include a personal history or family history, severe obesity (BMI>30 kg/m2) and systemic lupus erythematosus (SLE). There is no consensus about the possible role of varicose veins in VTE. Patients with a history of VTE or known thrombophilic states have an increased risk of VTE. HRT may add further to this risk. Personal or strong family history of thromboembolism, or recurrent spontaneous abortion, should be investigated in order to exclude a thrombophilic predisposition. Until a thorough evaluation of thrombophilic factors has been made or anticoagulant treatment initiated, use of HRT in such patients should be viewed as contraindicated. Those women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT. The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery. As in all postoperative patients, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilisation is liable	

	to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT four to six weeks earlier, if possible. Treatment should not be restarted until the woman is completely mobilised. If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g., painful swelling of a leg, sudden pain in the chest, dyspnea).	
Coronary artery disease (CAD) There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined oestrogen – progestagen or oestrogen-only HRT. The relative risk of CAD during use of combined oestrogen-progestagen HRT is slightly increased. As the baseline absolute risk of CAD is strongly dependent on age, the number of extra cases of CAD due to oestrogen-progestagen use is very low in healthy women close to menopause, but will rise with more advanced age.	Coronary artery disease (CAD) There is no evidence from randomised controlled trials of cardiovascolar benefit with continuous combined conjugated oestrogens and Medroxy Progesterone Acetate (MPA). Large clinical trials (WHI and HERS i.e. Heart and Estrogen/progestin Replacement Study) showed a possible increased risk of cardiovascular morbidity in the first year of use and no overall benefit. For other HRT products there are only limited data from randomised controlled trials examining effects benefit in cardiovascular morbidity or mortality. Therefore, it is uncertain whether these findings also extend to other HRT products.	

Ischaemic Stroke Combined oestrogen-progestagen and oestrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see section 4.8).	Stroke One large randomised clinical trial (WHI-trial) found, as a secondary outcome, an increased risk of ischaemic stroke in healthy women during treatment with continuous combined conjugated oestrogens and MPA. For women who do not use HRT, it is estimated that the number of cases of stroke that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 11 per 1000 women aged 60-69 years. It is estimated that for women who use conjugated oestrogens and MPA for 5 years, the number of additional cases will be between 0 and 3 (best estimate=1) per 1000 users aged 50-59 years and between 1 and 9 (best estimate=4) per 1000 users aged 60-69 years. It is unknown whether the increased risk also extends to other HRT products.	
Other conditions Oestrogens may induce or exacerbate symptoms of angioedema, in particular in women with hereditary angioedema.		
Drugs that inhibit the activity of hepatic microsomal drug metabolising enzymes, e.g. ketoconazole, may increase circulating levels of the active substances in Novofem.		**Interaction with other medicinal products and other forms of interaction**
Clinically, data on a limited number of exposed pregnancies indicate adverse effects of norethisterone on the foetus.	Clinically, data on a limited number of exposed pregnancies indicate no adverse effects of norethisterone on the foetus.	**Pregnancy and lactation**

Post-marketing experience: In addition to the above mentioned adverse drug reactions, those presented below have been spontaneously reported, and are by an overall judgment considered possibly related to Novofem treatment. Frequences of these adverse events cannot be estimated from the available data. • Neoplasms benign and malignant (including cysts and polyps) • Immune system disorders: Generalised hypersensitivity reactions (e.g. anaphylactic reaction / shock) • Psychiatric disorders: insomnia, anxiety, libido decreased, libido increased • Nervous system disorders: dizziness, stroke • Eye disorders: visual disturbances • Cardial disorders: myocardial infarction • Vascular disorders: hypertension aggravated • Gastrointestinal disorders: dyspepsia, vomiting • Hepatobiliary disorders: gallbladder disease, cholelithiasis, cholelithiasis aggravated, cholelithiasis reoccurrence • Skin and subcutaneous tissue disorders: seborrhoea, rash, angioneurotic oedema • Reproductive system and breast disorders: hyperplasia of endometrium,vulvovaginal pruritus • Investigations: weight decreased, blood pressure increased • Other adverse reactions have been reported in association with oestrogen/progestagen treatment: • Skin and subcutaneous disorders : alopecia, choloasma, erythema multiforme, erythema nodosum, haemorrhagic eruption and vascular purpura. • Probable dementia over the age of 65 (see section 4.4).	**Post-marketing experience:** In addition to the above mentioned adverse drug reactions, those presented below have been spontaneously reported, and are by an overall judgment considered possibly related to Novofem treatment. The reporting rate of these spontaneous adverse drug reactions is very rare: (<1/10,000 patient years). Post-marketing experience is underreporting especially with regard to trivial and well known adverse drug reactions. The presented frequencies should be interpreted in that light. Reproductive system and breast disorders: Hyperplasia of endometrium (for further information see section 4.4.) Skin and subcutaneous tissue disorders: Hirutism. Other adverse reactions have been reported in association with oestrogen/progestagen treatment: Estrogen-dependent neoplasms benign and malignant, e.g. endometrial cancer. Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among hormone replacement therapy users than among non-users. For further information, see under section 4.3 Contraindications and 4.4 Special Warnings	**Undesirable effects**

	and Precautions for Use. Myocardial infarction and stroke Skin and subcutaneous disorders : choloasma, erythema multiforme, erythema nodosum, haemorrhagic eruption and vascular purpura. Probable dementia (see under Special Warnings and Precautions for Use). Gall bladder disease.	
Endometrial Cancer risk The endometrial cancer risk is about 5 in every 1,000 women with a uterus not using HRT. In women with a uterus, use of oestrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see section 4.4). Depending on the duration of oestrogen-only use and oestrogen dose, the increase in risk of endometrial cancer in epidemiological studies varied from between 5 and 55 extra cases diagnosed in every 1,000 women between the ages of 50 and 65. Adding a progestagen to oestrogen-only therapy for at least 12 days per cycle can prevent this increased risk. In the Million Women Study the use of 5 years of combined (sequential or continuous) HRT did not increase risk of endometrial cancer (RR of 1.0 (0.8-1.2)).	**Endometrial Cancer** In women with an intact uterus, the risk of endometrial hyperplasia and endometrial cancer increases with increased duration of use of unopposed oestrogens. According to data from epidemiological studies, the best estimate of risk is that for women not using HRT, about 5 in every 1000 are expected to have endometrial cancer diagnosed between the ages of 50 and 65. Depending on the duration of treatment and oestrogen dose, the reported increase in endometrial cancer risk among unopposed oestrogen users varies from 2 to 12 fold greater compared to non users. Adding progestagen to oestrogen-only therapy greatly reduces this risk.	
Ovarian cancer risk 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 2,500 users		
Risk of venous thromboembolism HRT is associated with a 1.3- to 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 below..		
Risk of coronary artery disease The risk of coronary artery disease is slightly increased in users of combined oestrogen-progestagen HRT over the age of 60 (see section 4.4).		
Risk of ischaemic stroke The use of oestrogen-only and oestrogen-progestagen therapy 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 the baseline risk is strongly agedependent. The overall risk of stroke in women who use HRT will increase with age (see section 4.4).		