ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTH OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, APPLICANTS / MARKETING AUTHORISATION HOLDER IN THE MEMBER STATES

Member State	**Marketing Authorisation Holder**	**Applicant**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Austria		Novo Nordisk Pharma GmbH Opernring 3-5 A-1010 Vienna Austria	Noviana 0,5mg/0,1mg Filmtabletten	Estradiol (as hemihydrate) 0.5 mg + Norethisterone acetate 0.1 mg	Film-coated tablets	Oral use
Belgium		Novo Nordisk Pharma N.V Boulevard International 55/6, B-1070 Brussel Belgium	Activelle minor comprimés pelliculés	Estradiol (as hemihydrate) 0.5 mg + Norethisterone acetate 0.1 mg	Film-coated tablets	Oral use
Bulgaria		Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark	Eviana филмирани таблетки	Estradiol (as hemihydrate) 0.5 mg + Norethisterone acetate 0.1 mg	Film-coated tablets	Oral use
Czech Republic		Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark	Noviana potahované tablety	Estradiol (as hemihydrate) 0.5 mg + Norethisterone acetate 0.1 mg	Film-coated tablets	Oral use
Denmark		Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark	Activelle *low* filmovertrukne tabletter	Estradiol (as hemihydrate) 0.5 mg + Norethisterone acetate 0.1 mg	Film-coated tablets	Oral use
Estonia		Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark	Activelle	Estradiol (as hemihydrate) 0.5 mg + Norethisterone acetate 0.1 mg	Film-coated tablets	Oral use
Finland		Novo Nordisk A/S Novo Allé DK-2880 Bagsværd	Activelle 0,5 mg/0,1 mg tabl.	Estradiol (as hemihydrate) 0.5 mg + Norethisterone acetate 0.1 mg	Film-coated tablets	Oral use

Member State	**Marketing Authorisation Holder**	**Applicant**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
		Denmark				
France		Novo Nordisk Pharmaceutique S.A. 30 Rue De Valmy FR-92936 Paris La Defence Cedex France	Activelle 0,5 mg/0,1 mg comprimé pelliculé	Estradiol (as hemihydrate) 0.5 mg + Norethisterone acetate 0.1 mg	Film-coated tablets	Oral use
Germany		Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark	Noviana	Estradiol (as hemihydrate) 0.5 mg + Norethisterone acetate 0.1 mg	Film-coated tablets	Oral use
Hungary		Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark	Noviana filmtabletta	Estradiol (as hemihydrate) 0.5 mg + Norethisterone acetate 0.1 mg	Film-coated tablets	Oral use
Iceland		Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark	Activelle *low* 0.5 mg/0.1 mg tablets filmuhúðaðar töflur	Estradiol (as hemihydrate) 0.5 mg + Norethisterone acetate 0.1 mg	Film-coated tablets	Oral use
Ireland		Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark	Activelle Tablets	Estradiol (as hemihydrate) 0.5 mg + Norethisterone acetate 0.1 mg	Film-coated tablets	Oral use
Italy		Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark	Activelle 0,5 mg/0,1 mg compresse film-rivestite	Estradiol (as hemihydrate) 0.5 mg + Norethisterone acetate 0.1 mg	Film-coated tablets	Oral use
Latvia		Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark	Noviana 0,5 mg/0,1 mg apvalkotās tabletes	Estradiol (as hemihydrate) 0.5 mg + Norethisterone acetate 0.1 mg	Film-coated tablets	Oral use

Member State	Marketing Authorisation Holder	Applicant	(Invented) Name	Strength	Pharmaceutical Form	Route of administration
Lithuania		Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark	Activelle	Estradiol (as hemihydrate) 0.5 mg + Norethisterone acetate 0.1 mg	Film-coated tablets	Oral use
Luxembourg		Novo Nordisk Pharma N.V Riverside Business Park Boulevard International BE-1070 Brussels Belgium	Activelle comprimés pelliculés	Estradiol (as hemihydrate) 0.5 mg + Norethisterone acetate 0.1 mg	Film-coated tablets	Oral use
Netherlands		Novo Nordisk Farma B.V. Flemingweg 18 NL-2408 AV Alphen a/d Rijn Netherlands	Activelle filmomhulde tabletten	Estradiol (as hemihydrate) 0.5 mg + Norethisterone acetate 0.1 mg	Film-coated tablets	Oral use
Norway		Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark	Noviana 0,5 mg/0,1 mg tablett filmdrasjert	Estradiol (as hemihydrate) 0.5 mg + Norethisterone acetate 0.1 mg	Film-coated tablets	Oral use
Portugal		Novo Nordisk, A/S DNK Novo Allé, DK-2880 Bagsvaerd Denmark	Activelle	Estradiol (as hemihydrate) 0.5 mg + Norethisterone acetate 0.1 mg	Film-coated tablets	Oral use
Romania		Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark	Noviana comprimate filmate	Estradiol (as hemihydrate) 0.5 mg + Norethisterone acetate 0.1 mg	Film-coated tablets	Oral use
Slovak Republic		Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark	Noviana	Estradiol (as hemihydrate) 0.5 mg + Norethisterone acetate 0.1 mg	Film-coated tablets	Oral use

Member State	**Marketing Authorisation Holder**	**Applicant**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Slovenia		Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark	Noviana filmsko obložene tablete	Estradiol (as hemihydrate) 0.5 mg + Norethisterone acetate 0.1 mg	Film-coated tablets	Oral use
Spain		Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark	Activelle 0,5 mg/ 0,1 mg comprimidos recubiertos de película	Estradiol (as hemihydrate) 0.5 mg + Norethisterone acetate 0.1 mg	Film-coated tablets	Oral use
Sweden	Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark		Activelle	Estradiol (as hemihydrate) 0.5 mg + Norethisterone acetate 0.1 mg	Film-coated tablets	Oral use
United Kingdom		Novo Nordisk Pharma Ltd Broadfield Park Brighton Road UK- RH11 9RT Crawley West Sussex United Kingdom	Noviana film-coated tablets	Estradiol (as hemihydrate) 0.5 mg + Norethisterone acetate 0.1 mg	Film-coated tablets	Oral use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF ACTIVELLE AND ASSOCIATED NAMES (SEE ANNEX I)

Activelle 0.5 mg/0.1 mg is a continuous combined hormone replacement therapy (HRT) product containing 0.5 mg estradiol (E2) and 0.1 mg norethisterone acetate (NETA). It is intended for once daily administration to postmenopausal women with an intact uterus. It is a lower strength with a lower oestrogen/progestogen ratio than the currently approved Activelle, which contains 1 mg E2 and 0.5 mg NETA.

The referral under article 29(4) of directive 2001/83/EC was notified to the CHMP on March 3rd, 2008 as Germany and France did not consider the application acceptable. Both considered the endometrial safety of Activelle 0.5 mg/0.1 mg to be insufficiently demonstrated according to the CHMP guideline for HRT products (EMEA/CHMP/021/97 rev 1). A list of questions highlighting the issues to be discussed during this procedure was finalised on the 19th of March, 2008. The two issues discussed were as follows:

Endometrial Safety

The applicant/MAH was asked to demonstrate the endometrial safety of Activelle 0.5mg/0.1mg for the following reasons:

- The endometrial safety data is not in accordance with the European guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in post menopausal women (EMEA/CHMP/021/97 rev1).

- The endometrial safety data was extrapolated from another combination containing 1.0 mg estradiol and 0.1mg norethisterone acetate (NETA). In this study, the upper limit of the two-sided 95% CI of the incidence of endometrial hyperplasia was higher than the upper limit of 2%, and is therefore not considered acceptable.

-The endometrial safety of the combination of oestrogen and progestogen for the new ratio of 0.5mg/0.1mg cannot be extrapolated from the already licensed dose of Activelle, which contains 1mg estradiol and 0.5mg NETA. In the already licensed dose of Activelle, the ratio between NETA and E2 is 1:2, while this ratio is 1:5 in the new strength of Activelle.

Summary of CHMP Opinion

Activelle 0.5 mg/0.1 mg is a continuous combined HRT that contains the half dose of estradiol (E2) and the fifth of the dose of norethisterone acetate (NETA) that in the known fixed combination Activelle (E2 1 mg/NETA 0.5 mg). This means that the doses of E2 and NETA are decreased by 50% and 80%, respectively. Therefore, this new product contains a known progestogen at a lower dose than the known marketed dose, and a new ratio oestrogen/progestogen (1:5 instead of 1:2).

According to the guideline on clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women (EMEA/CHMP/021/97 Rev. 1) endometrial safety has to be demonstrated unequivocally before approval. It states that “for a new combination of oestrogen/progestogen (e.g. new administration scheme or new strength) or a new progestogen in a fixed combination, endometrial data are required, except for a known progestogen, with the same administration route and the same progestogen dose as in known fixed combination with oestrogen, where data on endometrial safety can be extrapolated from the fixed combination if exposure to the oestrogen is similar or lower”.

According to this recommendation, the applicant provided data from a trial (KLIM/PD/7/USA) which studied endometrial safety of the combination of E2 1 mg and NETA 0.1 mg. However, the some members of the CHMP noted that this trial failed to demonstrate the endometrial safety of the combination of E2 1 mg and NETA 0.1 mg, as the upper limit of the two-sided 95% confidence

interval of the observed frequency of endometrial hyperplasia was 2.90% and then exceeded the acceptable limit of 2%.

- Pooled data from several recently authorized sequential and continuous oestrogen/progestin HRT combinations in Europe show that the incidence of hyperplasia or more serious adverse endometrial outcomes was approximately 0.26% during the first year of treatment, that is well under the observed hyperplasia incidence of 0.8% in the KLIM/PD/7/USA trial. A new combination should not induce a higher frequency of hyperplasia as compared to the recently authorised combinations.
- The proportion of proliferative endometrium (71%) was higher, on the contrary the proportion of atrophic endometrium was lower (19%) than expected for a continuous combination. Moreover, one endometrial sample from a woman who received the E2 1 mg/NETA 0.1 mg combination was evaluated as "disordered proliferative" state. According to the European guideline, the endometrial biopsies should be classified, according to standardized criteria into the general classes of atrophic, proliferative, secretory, hyperplasia without atypia, hyperplasia with atypia, cancer and others. The class "disordered proliferative" used in study KLIM/PD/7/USA is not well defined and not usually recognized. It corresponds to abnormal endometrium and distinction from hyperplasia is not so clear.
- For the calculation of the incidence rate of endometrial hyperplasia and the two-sided 95 % confidence interval, in case of insufficient tissue obtained by biopsy and endometrial thickness $\geq$ 5 mm, the biopsy should be repeated or patient excluded from the calculation. In the present study, 7 samples had insufficient tissue and endometrial thickness > 4mm (the cut-off point for endometrial thickness was 4 mm). Consequently, these 7 samples should have been excluded from the final calculation.

Taking into account the points above, the some CHMP were of the opinion that endometrial safety of Activelle 0.5 mg/0.1 mg could not be supported by the KLIM/PD/7/USA trial.

However, a majority of CHMP members endorsed the applicant/MAH's approach to provide a very low dose alternative of combined continuous HRT. Given that there are studies demonstrating negative effects of combined HRT on the risk of breast cancer and cardiovascular complications, the general recommendation for HRT is to only treat women with severe symptoms, negatively affecting their quality of life.

The majority of the CHMP considered that the applicant/MAH had adequately justified why an endometrial biopsy study on the exact dose was not performed, unlike with Activelle 0,5mg/0,1mg. Based on several other studies of various doses of 1) unopposed oestrogens, 2) oestrogen-progestogen sequential combinations and 3) oestrogen-progestogen continuous combinations, the CHMP considered it reasonable and scientifically acceptable to extrapolate that this low dose continuous oestrogen-progestogen combination would result in a considerably lower rate of endometrial hyperplasia than seen with a combination containing twice the oestrogen dose.

In a systematic review of 30 randomized controlled trials, unopposed moderate or high dose oestrogen therapy, when compared to placebo, was associated with a significant increase in rates of endometrial hyperplasia with increasing rates at longer duration of treatment (Lethaby et al. Cochrane database of systematic reviews 2004;3). In this review, progestogen addition as continuous therapy was more effective than sequential therapy in reducing the risk of endometrial hyperplasia at longer duration of treatment. There was evidence of a higher incidence of hyperplasia when the progestogen was given every three months compared to when the progestogen was given sequentially every month. There was no significant difference in the rate of endometrial hyperplasia of continuous oestrogen-progestogen combinations in comparison with placebo after 12 and 24 months. This systematic review therefore supports that a continuous combined low dose regimen, as in Activelle 0,5mg/0,1mg, would provide sufficient endometrial protection.

Additional data on effects of continuous oestrogen –progestogen combined products on emdometrial hyperplasia.

The applicant was asked to provide any additional data, from clinical and observational studies, of relevance for the effects of continuous oestrogen-progestogen combined products on endometrial hyperplasia or endometrial cancer.

Summary of CHMP's Opinion

The CHMP noted that the applicant had provided the following arguments to support the endometrial safety of Activelle 0.5 mg/0.1 mg:

a. the proliferative effect of unopposed oestrogens on the endometrium is dose-dependant,
b. this proliferative effect of unopposed oestrogens is time-dependant, especially for high oestrogen doses,
c. continuous combined therapy over long duration is more protective that sequential therapy in the prevention of endometrial hyperplasia or carcinoma.

a. Dose-dependency of the proliferative effect of unopposed oestrogens

The dose-dependency of the proliferative effect of unopposed oestrogens on the endometrium was sustained by data from the KLIM/PD/11/USA trial for E2 (0.5 mg and 1 mg) and from Pickar et al for conjugated equine oestrogens (CEE, 0.3 to 0.625 mg).

- KLIM/PD/11/USA study:

  This study focused on prevention of osteoporosis but endometrial safety of unopposed E2 0.5 mg or 1 mg during 2 years was also assessed. It should be noted that sample size was very small (22 to 29 women), and no 95% confidence intervals for the incidence of hyperplasia are stated. It can also be noticed that the monitoring of the endometrial thickness by pelvic ultrasound showed a significant increase, even with 0.5 mg E2, which was not reported in the placebo group. Thus, in spite of the dose-related increase in incidence of hyperplasia, data could be considered insufficient to draw definite conclusions regarding endometrial safety of E2 0.5 mg.

- Pickar J.H. et al.:

  The objective of this study was to determine the endometrial safety of 2 years of treatment with low CEE doses (0.3, 0.45 and 0.625 mg). Data suggest a dose-response relationship between unopposed-CEE and risk of hyperplasia. As for the KLIM/PD/11/USA trial, sample size may be considered too low to draw definite conclusion with regard to endometrial safety.

In conclusion, the CHMP agreed that the proliferative effect of unopposed oestrogens on endometrium is dependent on the dose of oestrogens. However, some CHMP members considered that even if the observed hyperplasia incidence with the new dose E2 0.5 mg/NETA 0.1 mg should be lower than that observed with the E2 1mg/NETA 0.1mg combination, it is not unequivocally demonstrated that it will be in an acceptable range regarding the European guideline.

b. Duration-dependency of the proliferative effect of unopposed oestrogens

It is well established that the use of unopposed oestrogens in women with an intact uterus is associated with a gradually increasing incidence of hyperplasia with duration of treatment. However, some CHMP members were of the opinion that the data provided are insufficient to support that it is not the case with 0.5 mg E2. The sample size of the KLIM/PD/11/USA study may be considered too small to draw any definite conclusion regarding endometrial safety of E2 0,5 mg, even for 2 year-treatment. In Pickar J.H. et al, the relationship between treatment duration and incidence of hyperplasia was also observed with the low dose of 0.3 mg CEE.

c. Continuous combined therapy versus sequential therapy in the prevention of endometrial hyperplasia or carcinoma

The Cochrane review (Lethaby et al 2004) and analysis of available observational data (Anderson 2003, Beresford 97, Jain 2000, Hill 2000, Hully 98, MWS 2005, Newcomb 2003, Pike 97, Pukkala 2001, Weiderpass 99) suggest that addition of progestogen for at least 12 days per cycle reduces, but may not completely eliminate, the increased incidence of endometrial cancer caused by unopposed oestrogens; and that combined continuous HRT does not increase the risk of endometrial cancer. However, the CHMP noted that the strengths studied did not include E2 0.5 mg/NETA 0.1 mg. The only trial that studied the 0.1 mg NETA dose was the Novo Nordisk study KLIM/PD/7/USA , which some CHMP members considered to be inconclusive. Therefore, data from higher dose of NETA or other progestogens may not be extrapolated to the NETA 0.1 mg dose.

Taking the above arguments on board, the majority of CHMP members were of the opinion that the data presented demonstrate the importance of types of oestrogen-progestogen regimens for the association with endometrial cancer risk. These data, along with data on effects on endometrial hyperplasia, convincingly support the assumption that a continuous combined regimen protects the endometrium from both hyperplasia and neoplasia, a protective effect that seems to be both relative and absolute (i.e. conferring a lower risk than for untreated women) and that seems to increase with duration of intake. This observation is also consistent with the known pharmacodynamic effects of added progestogens on the endometrium, e.g. down regulation of oestrogen receptor (ER) levels and endometrial atrophy. On the basis of all these data, the majority of the CHMP was of the opinion that Activelle 0.5 mg estradiol/0.1 mg NETA is safe in terms of endometrial hyperplasia and neoplasia risk and that it offers a needed low-dose hormone replacement alternative with a positive benefit-risk.

GROUNDS

Whereas

- the endometrial safety of Activelle 0.5mg estradiol/0.1mg NETA product is sufficiently supported from the submitted data.

- on the level of endometrial hyperplasia, the trial on the 1 mg estradiol/0.1 mg NETA product indicates an adequate protective effect, albeit with an upper confidence limit of the hyperplasia rate estimate exceeding recommendation in the guideline.

- the risk of hyperplasia in Activelle 0.5 mg estradiol/0.1 mg NETA is lower than for the 1 mg estradiol/0.1 mg NETA product, containing one half of the dose as compared with the commercially available HRT product.

- the addition of a progestogen for 12 days of a monthly treatment cycle is considered sufficient to protect the endometrium from an excess risk of hyperplasia (and ultimately endometrial cancer), and even longer periods, and a continuous combination will confer increasing protective effects.

the CHMP has recommended the granting of the Marketing Authorisation(s) for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Activelle and associated names (see Annex I).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Activelle and associated names (see Annex I) 0.5 mg/0.1 mg film-coated tablets
[See Annex I – To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Estradiol 0.5 mg (as hemihydrate) and norethisterone acetate 0.1 mg.

Excipient: Each film-coated tablet contains lactose monohydrate 37.5 mg.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
White, round, biconvex tablets with a diameter of 6 mm. The tablets are engraved with "NOVO 291" on one side and the "APIS" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hormone Replacement Therapy (HRT) for oestrogen deficiency symptoms in women more than one year after menopause.

The experience of treating women older than 65 years is limited.

4.2 Posology and method of administration

Activelle is a continuous combined hormone replacement therapy intended for use in women with an intact uterus. One tablet should be taken orally once a day without interruption, preferably at the same time every day.

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see also section 4.4) should be used.

A switch to a higher dose product, e.g. Activelle 1 mg/0.5 mg tablets, should be considered if the response after three months is insufficient for satisfactory symptom relief.

In women with amenorrhea and not taking HRT or women transferring from another continuous combined HRT product, treatment with Activelle may be started on any convenient day. In women transferring from sequential HRT regimens, treatment should start right after their withdrawal bleeding has ended.
If the patient has forgotten to take a tablet, the tablet should be taken as soon as possible within the next twelve hours. Forgetting a dose may increase the likelihood of breakthrough bleeding and spotting.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients
- Known, past or suspected breast cancer
- Known or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer)

- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction)
- Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal
- Porphyria

4.4 Special warnings and precautions for use

For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk.

Medical examination/follow-up

Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and, by the contraindications and warnings for use. During treatment periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse (see section below "Breast cancer"). Investigations, including mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Conditions which need supervision

If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with Activelle in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- A history of, or risk factors for, thromboembolic disorders (see below)
- Risk factors for oestrogen dependent tumours, e.g. 1st degree heredity for breast cancer
- Hypertension
- Liver disorders (e.g. liver adenoma)
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or (severe) headache
- Systemic lupus erythematosus
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis

Reasons for immediate withdrawal of therapy

Therapy should be discontinued in case a contra-indication (see section 4.3) is discovered and in the following situations:

- Jaundice or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine-type headache

Endometrial hyperplasia

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 biopsy to exclude endometrial malignancy.

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 apparent 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 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 medroxyprogesterone acetate (CEE + MPA) product used was associated with breast cancers that were slightly larger in size and more frequently had local lymph node metastases compared to placebo.

HRT, especially oestrogen-progestagen combined treatment, may increase the density of mammographic images which may adversely affect the radiological detection of breast cancer.

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 epidemiological studies found a two- to threefold higher risk for users compared with non-users. 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 year 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 years. The occurrence of such an event is more likely in the first year of HRT than later.

Generally recognised risk factors for VTE include a personal history or family history, severe obesity (Body Mass Index > 30 kg/m^2) 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 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 cardiovascular benefit with continuous combined conjugated oestrogens and medroxyprogesterone acetate (MPA). Two 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 in cardiovascular morbidity or mortality. Therefore, it is uncertain whether these findings also extend to other HRT products.

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.

Ovarian cancer

Long-term (at least 5-10 years) use of oestrogen-only HRT products in hysterectomised women has been associated with an increased risk of ovarian cancer in some epidemiological studies. It is uncertain whether long-term use of combined HRTs confers to a different risk than oestrogen-only products.

Other conditions

Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed. Patients with terminal renal insufficiency should be closely observed, since it is expected that the level of circulating active ingredients in Activelle will increase.

Women with pre-existing hypertriglyceridemia 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 radio-immunoassay) 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 biological active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-I-antitrypsin, and ceruloplasmin).

There is no conclusive evidence for improvement of cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using continuous combined CEE and MPA after the age of 65. It is unknown whether the findings apply to younger post-menopausal women or other HRT products.

Activelle contains lactose monohydrate. Patients with any of the following rare hereditary diseases should not take this medicine: galactose intolerance, lactase deficiency or glucose-galactose malabsorption.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of oestrogens and progestagens 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, carbamazepin) 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 and progestagens.

Clinically, an increased metabolism of oestrogens and progestagens may lead to decreased effect and changes in the uterine bleeding profile.

Active substances that inhibit the activity of hepatic microsomal drug metabolizing enzymes e.g. ketoconazole, may increase circulating levels of the active substances in Activelle.

4.6 Pregnancy and lactation

Activelle is not indicated during pregnancy.
If pregnancy occurs during medication with Activelle, treatment should be withdrawn immediately.

Data on a limited number of exposed pregnancies indicate adverse effects of norethisterone on the foetus. At doses higher than normally used in OC and HRT formulations masculinisation of female foetuses was observed.

The results of most epidemiological studies to date relevant to inadvertent foetal exposure to combinations of oestrogens and progestagens indicate no teratogenic or foetotoxic effect.

Lactation

Activelle is not indicated during lactation

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The most frequently reported adverse reaction in the clinical trial with Activelle was vaginal bleeding. 11% of women at month 1, 15% of women at month 4 and 11 % of women at the end of the 6 month trial reported bleeding or spotting. All adverse reactions observed with a higher frequency in patients treated with Activelle compared to placebo and which on an overall judgement are possible related to treatment are presented below.

System organ class	Very common ≥1/10	Common ≥1/100; <1/10	Uncommon ≥1/1,000; <1/100	Rare ≥1/10,000; <1/1,000
Infections and infestations		Vulvovaginal mycotic infection, see also "Reproductive system and breast disorders		
Immune system disorders			Hypersensitivity, see also "Skin and subcutaneous tissue disorders	
Metabolism and nutrition disorders			Fluid retention, see also "General disorders and administration site conditions	
Psychiatric disorders			Depression or depression aggravated Nervousness	
Nervous system disorders		Headache	Migraine Dizziness	
Gastrointestinal disorders		Abdominal pain Nausea	Abdominal distension Dyspepsia	
Skin and subcutaneous tissue disorders			Pruritus or urticaria Alopecia Acne	
Musculoskeletal and connective tissue disorders		Back pain Neck pain Pain in extremity	Leg cramps	
Reproductive system and breast disorders	Vaginal haemorrhage	Endometrial thickening Vulvovaginal mycotic infection	Breast pain Breast discomfort	

System organ class	Very common ≥1/10	Common ≥1/100; <1/10	Uncommon ≥1/1,000; <1/100	Rare ≥1/10,000; <1/1,000
General disorders and administration site conditions			Oedema peripheral	

Breast cancer:
According to evidence from a large number of epidemiological studies and one randomised placebo-controlled trial, the Women's Health Initiative (WHI), the overall risk of breast cancer increases with increasing duration of HRT use in current or recent HRT users.

For oestrogen-only HRT, estimates of relative risk (RR) from a reanalysis of original data from 51 epidemiological studies (in which >80% of HRT use was oestrogen-only HRT) and from the epidemiological Million Women Study (MWS) are similar at 1.35 (95%CI 1.21 – 1.49) and 1.30 (95%CI 1.21 – 1.40), respectively.

For oestrogen plus progestagen combined HRT, several epidemiological studies have reported an overall higher risk for breast cancer than with oestrogens alone.

The MWS reported that, compared to never users, the use of various types of oestrogen-progestagen combined HRT was associated with a higher risk of breast cancer (RR = 2.00, 95%CI 1.88 – 2.12) than use of oestrogens alone (RR = 1.30, 95%CI 1.21 – 1.40) or use of tibolone (RR=1.45, 95%CI 1.25 – 1.68).

The WHI trial reported a risk estimate of 1.24 (95%CI 1.01 – 1.54) after 5.6 years of use of oestrogen-progestagen combined HRT (CEE + MPA) in all users compared with placebo.

The absolute risks calculated from the MWS and the WHI trial are presented below:

The MWS has estimated, from the known average incidence of breast cancer in developed countries, that:

- For women not using HRT, about 32 in every 1000 are expected to have breast cancer diagnosed between the ages of 50 and 64 years.
- For 1000 current or recent users of HRT, the number of additional cases during the corresponding period will be
    - For users of oestrogen-only replacement therapy
        - Between 0 and 3 (best estimate = 1.5) for 5 years' use
        - Between 3 and 7 (best estimate = 5) for 10 years' use.
    - For users of oestrogen plus progestagen combined HRT,
        - Between 5 and 7 (best estimate = 6) for 5 years' use
        - Between 18 and 20 (best estimate = 19) for 10 years' use.

The WHI trial estimated that after 5.6 years of follow-up of women between the ages of 50 and 79 years, an additional 8 cases of invasive breast cancer would be due to oestrogen-progestagen combined HRT (CEE + MPA) per 10,000 women years.

According to calculations from the trial data, it is estimated that:

- For 1000 women in the placebo group,
    - About 16 cases of invasive breast cancer would be diagnosed in 5 years.
- For 1000 women who used oestrogen + progestagen combined HRT (CEE + MPA), the number of additional cases would be
    - Between 0 and 9 (best estimate = 4) for 5 years' use.

The number of additional cases of breast cancer in women who use HRT is broadly similar for women who start HRT irrespective of age at start of use (between the ages of 45-65) (see section 4.4).

Endometrial cancer:

In women with an intact uterus, the risk of endometrial hyperplasia and endometrial cancer increases with increasing duration of use of unopposed oestrogens. According to data from epidemiological studies, the best estimate of the 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 with non-users. Adding a progestagen to oestrogen-only therapy greatly reduces this increased risk.

Post marketing experience:

In addition to the above mentioned adverse drug reactions, those presented below have been spontaneously reported, and are by an overall judgement considered possibly related to Activelle 1 mg/0.5 mg treatment. The reporting rate of these spontaneous adverse drug reactions is very rare (<1/10,000 patient years). Post-marketing experience is subject to underreporting especially with regard to trivial and well known adverse drug reactions. The presented frequencies should be interpreted in that light:

- Neoplasms benign and malignant (incl. cysts and polyps): Endometrial cancer
- Psychiatric disorders: Insomnia, anxiety, libido decreased, libido increased
- Nervous system disorders: Dizziness
- Eye disorders: Visual disturbances
- Vascular disorders: Hypertension aggravated
- Gastrointestinal disorders: Dyspepsia, vomiting
- Hepatobilitary disorders: Gallbladder disease, cholelithiasis, cholelithiasis aggravated, cholelithiasis re-occurrence
- Skin and subcutaneous tissue disorder: Seborrhoea, rash, angioneurotic oedema
- Reproductive system and breast disorders: Hyperplasia endometrial, vulvovaginal pruritus
- Investigations: Weight decreased, blood pressure increased

The following adverse reactions have been reported in the literature in association with oestrogen/progestagen treatment:

- Oestrogen-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 sections 4.3 and 4.4)
- Myocardial infarction and stroke
- Gall bladder disease
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura
- Probable dementia (For further information, see section 4.4)

4.9 Overdose

Overdose may be manifested by nausea and vomiting. Treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens and estrogens, fixed combinations, ATC code: G03FA01

Oestrogen and progestagen for continuous combined hormone replacement therapy (HRT).

Estradiol: The active ingredient, synthetic 17β-estradiol, is chemically and biologically identical to endogenous human estradiol. It substitutes for the loss of oestrogen production in menopausal women, and alleviates menopausal symptoms.

Norethisterone acetate: As oestrogens promote the growth of the endometrium, unopposed oestrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestagen reduces, but does not completely eliminate, the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

Relief of menopausal symptoms is achieved during the first few weeks of treatment. By Week 3, the decrease in mean number of moderate to severe hot flushes for the 0.5 mg estradiol treatment group was statistically significant ($p \leq 0.001$) when compared to the placebo group. This reduction remained until the conclusion of the study at week 24.

Activelle is a continuous combined HRT product containing 17β-estradiol and norethisterone acetate with the intent of avoiding the regular withdrawal bleeding associated with cyclic or sequential HRT. Amenorrhoea (no bleeding or spotting) was seen in 89% of the women in month 6 of treatment. Bleeding and/or spotting appeared in 11 to 15% of the women during the first six months of treatment.

5.2 Pharmacokinetic properties

Following oral administration of Activelle, 17β-estradiol is absorbed from the gastrointestinal tract, undergoes a first-pass metabolism in the liver and other enteric organs, and reaches a peak plasma concentration within 5-8 hours. After administration of two Activelle tablets, the average peak plasma

concentration was 24 pg/ml (CV 38 %). The half-life of 17β-estradiol is about 15 hours. It circulates bound to SHBG (37%) and to albumin (61%), while only approximately 1-2% is unbound.
Metabolism of 17β-estradiol, occurs mainly in the liver and gut but also in target organs, and involves the formation of less active or inactive metabolites, including estrone, catecholestrogens and several oestrogen sulphates and glucuronides. Conjugated oestrogens are excreted with the bile, where they are hydrolysed and reabsorbed (enterohepatic circulation), and mainly in urine in biologically inactive form.

After oral administration of an Activelle tablet, norethisterone acetate is rapidly absorbed and transformed to norethisterone (NET). It undergoes first-pass metabolism in the liver and other enteric organs, and reaches a peak plasma concentration of approximately 2.4 ng/ml CV 41 % (after administration of two Activelle tablets) within 0.5 -1.5 hour. The terminal half-life of NET is about 9-11 hours. NET binds to SHBG (36%) and to albumin (61%). The most important metabolites are isomers of 5α-dihydro-NET and of tetrahydro-NET, which are excreted mainly in the urine as sulfate or glucuronide conjugates.

The pharmacokinetics of estradiol is not influenced by norethisterone acetate.

The pharmacokinetics in the elderly has not been studied.

5.3 Preclinical safety data

The acute toxicity of estrogens is low. Due to the large differences between animal species and between animals and humans preclinical results are of limited value for predicting the effect on humans.
Animal studies have shown embryo-lethal effects of estradiol or estradiol valerate even at relatively low doses; malformations of the urogenital tract and feminization of male fetuses were observed.
Like other progestogens norethisterone causes virilization of female fetuses in rats and monkeys. At high doses of norethisterone embryo-lethal effects were observed.
Non-clinical data based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential reveal no special hazard for humans apart from those already discussed in other sections of the summary of product characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate
Maize starch
Hydroxypropylcellulose
Talc
Magnesium stearate

Film-coating:

Hypromellose
Triacetin
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate. Keep the container in the outer carton in order to protect from light.

6.5 Nature and contents of container

1 x 28 tablets or 3 x 28 tablets in calendar dial packs.

The calendar dial pack with 28 tablets consists of the following 3 parts:

- The base made of coloured non-transparent polypropylene
- The ring-shaped lid made of transparent polystyrene
- The centre-dial made of coloured non-transparent polystyrene

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

Detailed information on this medicinal product is available on the website of: {name of MS/Agency}[PIQ-QRD1]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Activelle and associated names (see Annex I) 0.5 mg/0.1 mg film-coated tablets
[See Annex I – To be completed nationally]

estradiol/norethisterone acetate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains:
estradiol 0.5 mg (as hemihydrate),
norethisterone acetate 0.1 mg

3. LIST OF EXCIPIENTS

Activelle contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
1 x 28 film-coated tablets
3 x 28 film-coated tablets

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C
Do not refrigerate
Keep the container in the outer carton, in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

Activelle 0.5 mg/0.1 mg

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

DISPENSER LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Activelle and associated names (see Annex I) 0.5 mg/0.1 mg film-coated tablets
[See Annex I – To be completed nationally]

estradiol/norethisterone acetate
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENT BY WEIGHT, BY VOLUME OR BY UNIT

28 film-coated tablets

6. OTHER

7. MANUFACTURER

Novo Nordisk A/S

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Activelle and associated names (see Annex I) 0.5 mg/0.1 mg film-coated tablets
[See Annex I – To be completed nationally]
Estradiol/norethisterone acetate

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again
- If you have further questions, ask your doctor or pharmacist
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT ACTIVELLE IS AND WHAT IT IS USED FOR

Activelle belongs to a group of hormone replacement therapy (HRT) medicines, called continuous combined HRT which are taken every day without interruptions.

Activelle is prescribed to relieve unpleasant symptoms like hot flushes, night sweats and vaginal dryness, which occur when the oestrogen levels decline and the periods stop (menopause).

Activelle is prescribed for women who have not had their womb removed, and whose periods stopped more than a year ago.

There is only limited experience of treating women older than 65 years with Activelle.

2. BEFORE YOU TAKE ACTIVELLE

Do not take Activelle
If any of the following applies to you, **talk to your doctor.** Do not start taking Activelle:
- If you are **allergic** (hypersensitive) to estradiol, norethisterone acetate or any of the other ingredients of Activelle (listed in section 6,"*Further information*").
- If you have or have had **breast cancer,** or if it is suspected
- If you have **cancer of the womb lining** (endometrium), or if such an oestrogen dependent cancer is suspected
- If you have any **vaginal bleeding,** which has not been diagnosed by your doctor
- If you have **endometrial hyperplasia** (excessive growth of the womb lining) that is not being treated
- If you have a **blood clot (**like deep vein thrombosis or lung embolism**)** or previously have had a blood clot without obvious cause, e.g. in connection with surgery or pregnancy
- If you have recently had a **heart attack**, **stroke,** or have **angina**
- If you have or have had a **liver disorder** and your liver tests have not returned to normal
- If you have **porphyria** (a liver enzyme disease)

Take special care with Activelle

If you have (or have had) any of the following conditions, **tell your doctor**. Your doctor may then want to follow your treatment up more closely. Rarely, these conditions may come back or get worse during treatment with Activelle:

- If you have any **condition affecting the womb lining**, such as myoma (benign tissue tumour), endometriosis (presence of womb lining tissue outside the womb) or have had endometrial hyperplasia (excessive growth of the womb lining)
- If you have **a history of blood clots** (thrombosis) or have risk factors for blood clots (these risk factors and symptoms for a blood clot are listed in section 4,"*Other side effects of combined HRT"*)
- If **any of your immediate family has had breast cancer**, or other cancers related to oestrogen (endometrial cancer)
- If you have **high blood pressure**
- If you have **a liver disorder** such as liver adenoma (a benign tumour)
- If you have **a kidney** or **heart disorder**
- If you have **diabetes** or **gallstone disease**
- If you have **epilepsy** or **asthma**
- If you get **migraines** or **severe headaches**
- If you have **systemic lupus erythematosus (SLE, autoimmune collagen disease, which may affect many organ systems)**
- If you have **high levels of fat in the blood** (hypertriglyceridemia)
- If you have **otosclerosis** (hearing loss sometimes linked to pregnancy).

Medical check-ups
Before you start taking Activelle, your doctor will inform you about the risks and benefits of the treatment (see also section 4, "*Other side effects of combined HRT*"). Before you start treatment and regularly during treatment, your doctor will evaluate whether Activelle is a suitable treatment for you. Your doctor will tell you how often you should go for periodic check-ups, taking into account your general state of health.
If you have any close relative (mother, sister, maternal or paternal grandmother), who has suffered from serious illness, e.g. blood clot or breast cancer, you might also be at increased risk. You should therefore always tell your doctor about any close relative suffering from serious illness, and you should also tell your doctor about any changes, you might find in your breasts.
As well as regular check-ups with your doctor, be sure to:
- Regularly **check your breasts** for any changes, such as dimpling or sinking of the skin, changes in the nipple, or any lumps you can see or feel
- Go for regular **breast screening** (mammography) and **cervical smear** tests.

If you **need a blood test**, tell your doctor that you are taking Activelle, since oestrogen can affect the results of certain laboratory tests.

If you are going to have surgery, talk to your doctor. You may need to stop taking these tablets 4 to 6 weeks before the operation, to reduce the risk of a blood clot. Your doctor will tell you when you can start treatment again.

Stop taking Activelle
If you are experiencing any of the following conditions below, stop taking Activelle, and contact your doctor immediately:
- If you get a **migraine-type headache** for the first time
- If you **develop yellow skin or eyes** (*jaundice*) or other liver problems
- If your **blood pressure goes up** while you're taking Activelle
- If you **become pregnant**
- If **any of the conditions** listed in section 2,"*Do not take Activelle",* occur.

Using other medicines
Some medicines may reduce the effects of Activelle:

- Medicines used for **epilepsy** (such as phenobarbital, phenytoin and carbamazepin)
- Medicines used for **tuberculosis** (such as rifampicin, rifabutin)
- Medicines used for **HIV infections** (such as nevirapine, efavirenz, ritonavir and nelfinavir)
- Herbal products containing **St John's Wort** (*Hypericum perforatum*).

Other medicines may increase the effects of Activelle:
- Medicines containing **ketoconazole** (a fungicide).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines including medicines obtained without a prescription, herbal medicines or other natural products.

Using Activelle with food and drink
The tablets can be taken with or without food and drink.

Pregnancy and breast-feeding
Do not take Activelle if you are pregnant or breast-feeding.

Driving and using machines
Activelle does not affect the use of any machines or the ability to drive safely.

Important information about some of the ingredients of Activelle:
Activelle contains lactose. If you have an intolerance to some sugars, contact your doctor before taking Activelle.

3. HOW TO USE ACTIVELLE

Always take Activelle exactly as your doctor has told you. Check with your doctor or pharmacist if you are unsure.

Take one tablet once a day, at about the same time each day
Take the tablet with a glass of water.

Take a tablet every day without stopping[PIQ-QRD2]**.** After you have used all 28 tablets in a calendar pack, go straight to using the next pack.

For instructions on the use of the calendar pack, see "USER INSTRUCTIONS" at the end of the package leaflet.

You may **start treatment with Activelle** on any convenient day. However, if you are switching from an HRT product where you have monthly bleeding, start your treatment straight after the bleeding has ended.

Your doctor should aim to prescribe the lowest dose for the shortest time that gives you relief from your symptoms. Talk to your doctor if your symptoms are not better after three months of treatment.

If you take more Activelle than you should
If you have taken more Activelle than you should, or if for example a child has taken Activelle accidentally, talk to your doctor or hospital to assess the risk and for advice. An overdose of Activelle could make you feel sick or vomit.

If you forget to take Activelle
If you forget to take your tablet at the usual time, take it within the next 12 hours. If more than 12 hours have gone by, start again as normal the next day. Do not take a double dose to make up for a forgotten tablet.

Forgetting a dose may increase the likelihood of breakthrough bleeding and spotting unless you have had your womb removed.

If you stop taking Activelle
If you want to stop taking Activelle, talk to your doctor first. Your doctor will explain the effects of stopping treatment and discuss other possibilities with you.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Activelle can have side effects, although not everybody gets them.

Bleeding with Activelle
Activelle will not cause regular monthly bleeding, but when first starting the tablets, many women experience slight vaginal bleeding or spotting. If you get breakthrough bleeding or spotting, it is usually nothing to worry about, especially during the first few months of taking HRT.
But contact your doctor as soon as possible:
- If bleeding carries on for more than the first few months
- If bleeding starts after taking HRT for a while
- If bleeding continues after stopping HRT.

Your doctor may ask you about any vaginal bleeding with Activelle at your regular check-ups. You may find it helpful to make a note of any bleedings in a diary.

The frequency of possible side effects listed below is defined using the following convention:
Very common (affects more than 1 user in 10)
Common (affects 1 to 10 users in 100)
Uncommon (affects 1 to 10 users in 1,000)
Rare (affects 1 to 10 users in 10,000)
Very rare (affects less than 1 user in 10,000)
Not known (frequency cannot be estimated from the available data).

Very common side effects
- Vaginal bleeding.

Common side effects
- Fungal infection of the genitals or vaginal inflammation
- Excessive growth of the womb lining (endometrial hyperplasia)
- Feeling sick
- Abdominal (stomach) pain
- Pain in back or neck
- Pain in arms or legs
- Headache.

Uncommon side effects
- Allergic reaction (hypersensitivity)
- Depression or worsening of existing depression
- Nervousness
- Dizziness
- Migraine (see "*Stop taking Activelle*" in section 2)
- Breast pain or breast discomfort
- Swelling or discomfort of the abdomen (stomach)
- Weight gain caused by fluid retention
- Swelling of arms and legs (peripheral oedema)
- Leg cramps

- Heartburn (dyspepsia)
- Acne
- Hair loss
- Itching or urticaria.

Other side effects of combined HRT

The following side effects have been reported after taking medicines containing oestrogen/progestagens.

Excessive growth of the womb lining (endometrial hyperplasia) and cancer of the womb lining (endometrial cancer)
In women with an intact womb, the risk of excessive growth of the womb lining (endometrial hyperplasia) is increased. Treatment with unopposed oestrogens for long periods of time also increases the risk of cancer of the lining of the womb (endometrial cancer). Adding a progestagen, such as in Activelle, greatly reduces this increased risk.

Breast cancer
Every woman is at risk of getting breast cancer whether or not she takes HRT. There is a small increase in this risk for women who have been using HRT for more than 5 years compared with women of the same age who have never used HRT. This risk increases with the duration of intake of HRT, but returns to normal within a few (at most five) years of having stopped HRT. The risk seems to be higher for women, who use oestrogen in combination with progestagen as compared to oestrogen alone.
To be able to detect a breast tumour as early as possible, it is important to regularly check your breasts for any changes and to discuss any changes with your doctor. Also go for regular health check, including mammography. If you are anxious for the risk of breast cancer, you should talk to your doctor about the risks and benefits of HRT.

Blood clots in the deep veins
Every woman is at risk of getting a blood clot whether or not she takes HRT.
HRT may increase the risk of blood clots 2-3 times in the veins, especially in the first year of treatment. These are not always serious, but they may need to be treated.
You are also more likely to get a blood clot:
- If you are very overweight
- If you have had a blood clot before, or have had any blood clotting problem that needed treatment with a medicine such as Warfarin
- If any of your close family has had blood clots
- If you have had a miscarriage
- If you are bed-ridden for a longer period through surgery, injury or illness
- If you have systemic lupus erythematosus (SLE, autoimmune collagen disease, which may affect many organ systems)

You may be at risk of having a blood clot if you get:
- Painful swelling in your leg
- Sudden chest pain
- Difficulty breathing.

See a doctor as soon as possible. Stop taking HRT until your doctor says you can take it again.

Heart disease
If you ever have had angina or heart attack, you should talk to your doctor about the risks and benefits of HRT.
There is no evidence of beneficial effects on the risks of cardiovascular disease with HRT in the menopause. Results from two clinical studies showed that women, who used another type of oestrogen/progestagen combination than the one in Activelle, had a slightly increased risk of cardiovascular disease in the first year of use.

For other HRT products there are only limited data from trials examining the effects on the risk of cardiovascular disease.

Stroke
There may be a slightly higher risk of having a stroke if you are taking HRT.
Other factors that also increase the risk of stroke are:
- Getting older
- High blood pressure
- Smoking
- Drinking too much alcohol
- An irregular heartbeat.

If you get:
- Unexplained migraine-type headaches, with or without disturbed vision.

See a doctor as soon as possible. Stop taking HRT until your doctor says you can.

Ovarian cancer
There are some evidence from clinical studies that use of oestrogen-only products for more than 5 years increases the risk of ovarian cancer among women who have had their womb removed. It is not yet known whether other types of HRT increase the risk in the same way.

Dementia
There is no evidence that HRT improves processes of remembering, learning and judging (cognitive function). From a clinical study there is some evidence for an increased risk of dementia among women older than 65 years, who started using another type of oestrogen/progestagen combination than the one in Activelle. It is not known whether these results also applies to women younger than 65 years when starting the treatment or to women taking other HRT preparations.

Gall bladder disease
Gall bladder disease has been reported after treatment with oestrogen/progestagen.

Effects on the skin
Brown pigmented patches in the face, redness of the skin including inflammation on the hands or the legs (erythema multiforme), hump rose or a bruise-like rash.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ACTIVELLE

Keep out of the reach and sight of children.

Do not use Activelle after the expiry date which is stated on the label and outer carton after "EXP". The expiry date refers to the last day of that month.

Do not store above 25°C.
Do not refrigerate.
Keep the container in the outer carton in order to protect from light.

Medicines should not be disposed of via waste water or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Activelle contains

- The active substances are estradiol and norethisterone acetate. Each tablet contains 0.5 mg estradiol (as hemihydrate) and 0.1 mg norethisterone acetate.
- Other ingredients are: Lactose monohydrate, maize starch, hydroxypropylcellulose, magnesium stearate, hypromellose, triacetin and talc.

What Activelle looks like and contents of the pack

The film-coated tablets are white, round with a diameter of 6 mm. The tablets are imprinted NOVO 291 on one side and the Novo Nordisk logo (an Apis bull) on the other side.

Pack sizes:
28 film-coated tablets
3 x 28 film-coated tablets
Not all pack sizes may be marketed.

Marketing authorisation holder and manufacturer

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This medicinal product is authorized in the Member States of the EEA under the following names:

Austria - Noviana 0,5mg/0,1mg filmtabletten
Belgium - Activelle minor comprimés pelliculés
Bulgaria - Noviana™ филмирани таблетки
Czech Republic - Noviana potahované tablety
Denmark - Activelle *low* filmovertrukne tabletter
Estonia - Activelle *low* 0,5 mg/0,1 mg õhukese polümeerikattega tablett
Finland - Activelle 0,5 mg/0,1 mg tabl.
France - Activelle 0,5 mg/0,1 mg comprimé pelliculé
Germany - Noviana
Hungary - Noviana filmtabletta
Iceland - Activelle® *low* 0.5 mg/0.1 mg tablets filmuhúðaðar töflur
Ireland - Activelle *low* 0.5mg/0.1mg film-coated tablets
Italy - Activelle® 0,5 mg/0,1 mg compresse film-rivestite
Latvia - Noviana 0,5 mg/0,1 mg apvalkotās tabletes
Lithuania - Activelle 0,5 mg / 0,1 mg plėvele dengtos tabletės
Luxembourg - Activelle minor comprimés pelliculés
The Netherlands - Activelle filmomhulde tabletten
Norway - Noviana 0,5 mg/0,1 mg tablett filmdrasjert
Portugal - 0,5mg Estradiol + 0.1 mg Acetato de Noretisterona Comprimidos revestidos por película
Romania – Noviana comprimate filmate
Slovenia - Noviana™ filmsko obložene tablete
Slovakia - Noviana filmom obalené tablety
Spain - Activelle 0,5 mg/ 0,1 mg comprimidos recubiertos de película
Sweden - Activelle 0,5 mg/0,1 mg filmdragerade tabletter
United Kingdom - Noviana film-coated tablets

[See Annex I – To be completed nationally]

This leaflet was last approved in

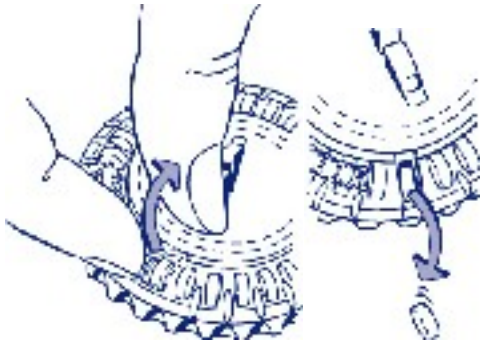
Detailed information on this medicine is available on the web site of {MA/Agency}[PIQ-QRD3]

USER INSTRUCTIONS

How to use the calendar pack

1. Set the day reminder
Turn the inner disc to set the day of the week opposite the little plastic tab.

2. How to take the first tablet
Break the plastic tab and tip out the first tablet.



3. Move the dial every day
On the next day simply move the transparent dial clockwise one space as indicated by the arrow. Tip out the next tablet. Remember to take only one tablet once a day.
You can only turn the transparent dial after the tablet in the opening has been removed.