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FRONT OFFICE FOOD AND PRODUCT SAFETY

RISK ASSESSMENT DERMAL CREAMS CONTAINING HORMONES

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Nederlandse samenvatting

Verschillende webshops verkopen hormooncrèmes die bedoeld zijn om overgangsklachten bij vrouwen te verminderen. Deze crèmes bevatten veelal progesteron, dehydroepiandrosteron (DHEA), estriol of pregnenolon. De crèmes vallen niet onder de wetgeving voor cosmetische producten of medicijnen maar onder de Warenwet. In de Warenwet worden farmacologische stoffen niet beoordeeld; dit gebeurt in de wetgeving over medicijnen. De NVWA wil graag weten of er een mogelijk risico voor de volksgezondheid is bij het gebruik van dit soort crèmes zonder medisch toezicht, en of er kwetsbare groepen of risicovolle scenario's bij het gebruik van de crèmes te identificeren zijn.

De interne blootstelling en eventuele gezondheidseffecten als gevolg van het gebruik van een hormooncrème hangt onder andere af van de dermale absorptie van het hormoon. Eenmaal opgenomen in het lichaam zijn eventuele (ongewenste) effecten afhankelijk van distributie door het lichaam en metabolisatie van de hormonen.

Er is weinig wetenschappelijke literatuur beschikbaar over hormooncrèmes. Zo is er weinig informatie over de dermale absorptie van de hormonen. Ook ontbreekt informatie over de effectiviteit van het gebruik van de crèmes tegen overgangsklachten. Op basis van beschikbare informatie over de hormooncrèmes en over geneesmiddelen die dezelfde hormonen bevatten is deze risicobeoordeling opgesteld.

Uit de beschikbare informatie kan geconcludeerd worden dat het gebruik van crèmes met DHEA of estriol mogelijk een risico vormt voor vrouwen in de menopauze. Zo zijn er bijvoorbeeld zorgen over mogelijke lokale ongewenste effecten. Een verhoogd risico op kanker wordt verwacht bij (ex-) patiënten met borstkanker en/of hormoongevoelige kanker. Andere kwetsbare groepen zijn vrouwen in de vruchtbare leeftijd, kinderen en adolescenten, patiënten met verschillende ziektebeelden (o.a. diabetes, trombose en ernstige leverfunctiestoornissen), en patiënten die medicatie gebruiken die effect kunnen hebben op het metabolisme (met name cytochroom P450 systeem).
Bij het gebruik van crèmes met pregnenolon of progesteron is de verwachting dat de dermale absorptie minimaal is. Echter, door het gebrek aan informatie en tegenstrijdige informatie over deze hormonen is er onzekerheid over de daadwerkelijke dermale absorptie en (ongewenste) effecten, en zijn risico's niet uit te sluiten.

Summary

Hormone containing dermal creams are available via web shops and are meant for women to reduce menopausal symptoms. The creams contain mostly progesterone, dehydroepiandrosterone (DHEA), estriol or pregnenolone. In the Netherlands, these creams are not within the scope of the

cosmetic- or drug regulations and consequently fall within the Commodities Act. Within the Commodities Act, pharmacological compounds are not assessed as this is covered by the drug regulations. The Netherlands Food and Consumer Product Safety Authority (NVWA) would like to know whether the use of hormone containing creams without medical supervision poses a risk to the public health, and whether vulnerable groups or high-risk scenarios can be identified.

Internal exposure and health effects following the use of a hormone cream depend on the dermal absorption of the hormone. As soon as the hormone is absorbed into the body, possible (undesired) effects depend on the distribution through the body and metabolism of the hormone.

In general, little scientific literature on hormone creams is available. For instance, information on the dermal absorption of hormones is frequently lacking. Also, there is no clear scientific evidence that using hormone creams (as mentioned in this risk assessment) will reduce menopausal symptoms. Due to the general lack of information about hormone creams, this this risk assessment has been prepared as well with available information of pharmaceutical products containing the hormones.

Based on the available data, it can be concluded that the use of creams containing DHEA or estriol may pose a risk for menopausal women as there are concerns for local undesirable effects. Also, an increased risk of cancer is expected in women with (a history of) breast cancer and estrogen-sensitive malignant tumors. Other identified vulnerable groups include fertile women, children and adolescents, patients including diabetics, people with thrombotic disorders, and people with severe hepatic impairment, and patients using pharmaceutical products which are involved in drug metabolism (in particular cytochrome P450).
In the case of creams containing pregnenolone or progesterone, limited absorption is expected. However, due to uncertainties about absorption and lack on information, it is not possible to rule out any risk.

Subject

Hormone containing dermal creams with a low concentration of progesterone, dehydroepiandrosterone (DHEA), estriol or pregnenolone are available via web shops and are meant for women to reduce menopausal symptoms. These creams are outside the scope of the cosmetic- or drug regulations and consequently fall within the Commodities Act ('Warenwet'). This means that possible risks in relation to the pharmacological active components (hormones) are not specifically assessed. The use of these creams, without medical control, could therefore pose a potential risk to public health.
The Netherlands Food and Consumer Product Safety Authority (NVWA) made an inventory of this market in the first quarter of 2018. All products that were found by an internet search were purchased through internet, including from internet shops located outside of the Netherlands. For each product, hormone levels were analyzed and reported together with the declared levels (see Annex I for an overview of the results). Directie Handhaven asked BuRO to assess potential risks to public health following declared use of these hormone containing dermal creams.

Additional information

As the hormone containing dermal creams are used without supervision by a physician, BuRO widens the scope of the subject by examining risks for vulnerable groups when using the creams. BuRO also asks to list possible risks in case of incorrect or unforeseen usage (e.g. overdosing and interactions with pharmaceutical products through combined use).
The aim of this survey was to obtain an overview of the available products and their hormone content; the analytical method was validated for 3 hormones. Based on the measurements it can be concluded that:

1. The analyzed hormone levels are lower compared to the declared concentrations of the creams: therefore, the use of declared concentrations will lead to a conservative risk assessment. The theoretical exposure from declared concentrations will be used as basis for the risk assessment.
2. The fact that the measured concentrations are lower than the declared concentration gives reason to assess the risk of overdosing: when the desired effect is not achieved with the prescribed use, excessive use by the consumer is a possible scenario.

Questions

Opinion on the following questions:

1. Is at exposure levels, based on the declared concentrations DHEA, estriol, pregnenolone, and progesterone and the prescribed use, a risk to public health expected?
2. Given the use without medical supervision, can vulnerable groups of high-risk scenarios be identified?

Elements to include in the answer:

1. Initially, the risk assessment can be performed using the highest declared concentrations of DHEA, estriol, pregnenolone, and progesterone. In case a risk is identified under these conditions, further refinement should be included.
2. Besides the use by the intended target group (women with menopausal symptoms), possible vulnerable groups should be included. Groups for discussion are amongst others: pregnant women (unborn child), young children, adolescents, men, and people with specific health issues (e.g. hormone (progesterone) related breast cancer).
3. Risks of overdosing (possibly encouraged in case of absence of desired effects) and the relevance of interaction with pharmaceutical products.

Conclusions

Risk assessment
In general, lack of data on (dermal absorption of) the discussed hormones and creams hampers a full risk assessment. This risk assessment is therefore based on available information on absorption, serum/plasma levels and clinical effects of the dermal creams and pharmaceutical products containing hormones, which resulted in the following conclusions per hormone for menopausal women (as the target population):

- DHEA
  Contradictory results in changes in serum concentrations following dermal application of DHEA were reported. One study reports using DHEA cream results in about the same serum levels compared to the use of a pharmaceutical product (ovule), therefore similar side effects might be expected, which include the development of cervical and uterine polyps, and weight fluctuations. There are concerns for possible local carcinogenic effects. Additional studies on the dermal absorption of DHEA and safety of the use of DHEA containing creams are required.
- Estriol
  No information on dermal absorption of estriol from dermal creams is available, hampering a firm conclusion on potential risk on the use of estriol containing creams. Some side effects are reported in the case of a vaginal cream. Additional studies on the safety of the use of estriol containing creams are required.
- Pregnenolone
  Although little data on dermal absorption is available, it is suggested that pregnenolone has a very limited dermal absorption. With regard to side effects and overdosing, no information is available. Additional studies are required to rule out any risk for menopausal women using pregnenolone containing creams.
- Progesterone
  Data on dermal absorption is controversial. It is expected that only sub-physiological levels of progesterone in menopausal women can be achieved using progesterone containing cream. Due to the general lack of adverse effects at sub-physiological levels, no adverse effects are expected for postmenopausal women with intrinsic low progesterone levels. However, additional studies are required to rule out any local or systemic risk for menopausal women using progesterone containing creams.

Noteworthy, both DHEA and pregnenolone are also available as dietary supplements. It is, however, outside the scope of this report to include these supplements in the current risk analysis.

Vulnerable groups
Despite the lack of information, based on the information files of pharmaceutical products, several vulnerable groups are identified:

- Women with (a history of) breast cancer and estrogen-sensitive malignant tumors (especially relevant for creams with DHEA or estriol)
- Premenopausal women/fertile women, including pregnant women (and the unborn child) and during breastfeeding
- Diabetics, people with hypertension, migraine, thrombotic disorders, severe hepatic impairment and several other conditions
- People using pharmaceutical products known to induce enzymes which are involved in drug metabolism (in particular cytochrome P450)
- Children and adolescents

Overdosing
No information is available on adverse effects or overdosing of hormone containing creams. Information on the use of hormone creams and interaction with other pharmaceutical products is also lacking. Therefore, the dermal creams are compared to pharmaceutical products containing the same hormone, and the information of the most comparable product is used for the risk assessment. Information files of the pharmaceutical products describe mild health effects following overdose.

Preface

Risk assessment of exogenous compounds is commonly based on four components: hazard identification, dose-response assessment, exposure assessment, and risk characterization. To indicate the potential harm of chemicals, reference values on their toxicity are used (among them lowest observed effect level (LOEL), lowest observed adverse effect level (LOAEL), derived no effect level (DNEL), no observed effect levels (NOEL), lethal doses (e.g. LD_{50}), acceptable daily intake (ADI), etc.). For endogenous chemicals, reference values are often lacking. In the case of hormones, the human body has several mechanisms to cope with unexpected elevations. Furthermore, levels of steroid hormones fluctuate naturally in order to regulate e.g. the menstrual cycle in women and several other (feedback) mechanisms. Due to the natural fluctuations and mechanisms to cope with increased levels, elevation of serum levels of steroid hormones will not immediately cause (acute) severe and/or irreversible adverse (toxic) health effects. More likely, following acute (high dose) and/or chronic exposure, side effects will occur, which are also observed in patients receiving steroid hormone(s) for medical reasons.

The current risk assessment on dermal application of steroid hormones is an example of performing risk characterization with endogenous chemicals. As no useful 'classic' relevant safety values are applicable for the selected hormones (dehydroepiandrosterone (DHEA), estriol (E3), pregnenolone (P5), and progesterone (P4)), this risk assessment is based on the comparison of serum and/or plasma levels and clinical effects of dermal creams and pharmaceutical products. Subsequently, the side effects and contra-indications of the most comparable pharmaceutical products are used as a good indication for those of the hormone containing dermal creams.

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Introduction

Background information on steroid hormones

Steroidogenesis is the biological process by which steroids are generated from cholesterol and transformed into other steroids, which includes the three types of sex hormones progestagens, androgens and estrogens. This process is illustrated in Figure 1. Classic steroidogenic tissues are the gonads, adrenal glands and placenta. Steroids can also be synthesized in the brain: neurosteroids that act locally to modify brain functions.
An overview of steroids (relevant for the present report) and their major hormone function is shown in Table 1. Hormonal changes during the ovulatory menstrual cycle, and differences in hormone concentration between pre-menopause and post-menopause are visualized in the paper by Hall and Philips (2005) [2].

Androgens

Androgens are a class of steroid hormones that regulates the development of male characteristics. In male, the major androgen is testosterone. Female ovaries and adrenal glands also produce levels of androgens that may prevent premature uterine contractions in pregnancy [3].

Progestagens

Progestagens are a class of steroid hormones with involvement in regulation of the menstrual cycle, maintenance of pregnancy, and preparation of the mammary glands for lactation and breastfeeding following parturition in women. Progesterone (P4) is the major and most important progestagen in the body. In men, progesterone affects spermiogenesis, sperm capacitation, and testosterone synthesis. Progesterone is produced from cholesterol with pregnenolone (P5) as a metabolic intermediate. Pregnenolone is known as the precursor to other steroids and not as an active steroid. Pregnenolone is lipophilic and readily crosses the blood brain barrier [4].

Estrogens

Estrogens are steroid hormones associated with the female reproductive organs. They promote the development of female secondary sexual characteristics and are also involved in the thickening of the endometrium and other aspects of regulating the menstrual cycle. While estrogen levels are significantly lower in men compared to females, estrogens also have important physiological roles in men [5]. In males, estrogen regulates certain functions of the reproductive system important to the maturation of sperm and libido.
The effects of decreasing estrogen levels may include wrinkling, dryness, atrophy, laxity, poor wound healing of the skin, as well as hot flashes, and vulvar atrophy [2, 6]. Estrogen replacement may ameliorate some of these effects.

The three major endogenous estrogens that have estrogenic hormonal activity include estrone (E1), estradiol (E2), and the final metabolite of the estrogen synthesis estriol (E3). All of these are synthesized from androgens, specifically testosterone and androstenedione, by the enzyme aromatase. Estrogens are in large part or completely synthesized locally in peripheral tissues from the precursor dehydroepiandrosterone (DHEA, see Figure 1), thus providing target tissues with the appropriate controls to adjust the formation and metabolism of estrogens according to local requirements. Estrogen hormone levels in the body are regulated by feedback mechanisms of estrogen on the hypothalamus and pituitary gland.

Table 1. *Classes of steroids in steroidogenesis*

Steroid	Major hormone and function
Androgens	Testosterone, contributes to development and maintenance of male secondary sex characteristic s
Progestagens	Progesterone, regulates cyclic changes of endometrium of the uterus
Estrogens	Estradiol, contributes to development and maintenance of female secondary sex characteristics

Table by Häggström et al. (2014) [1]

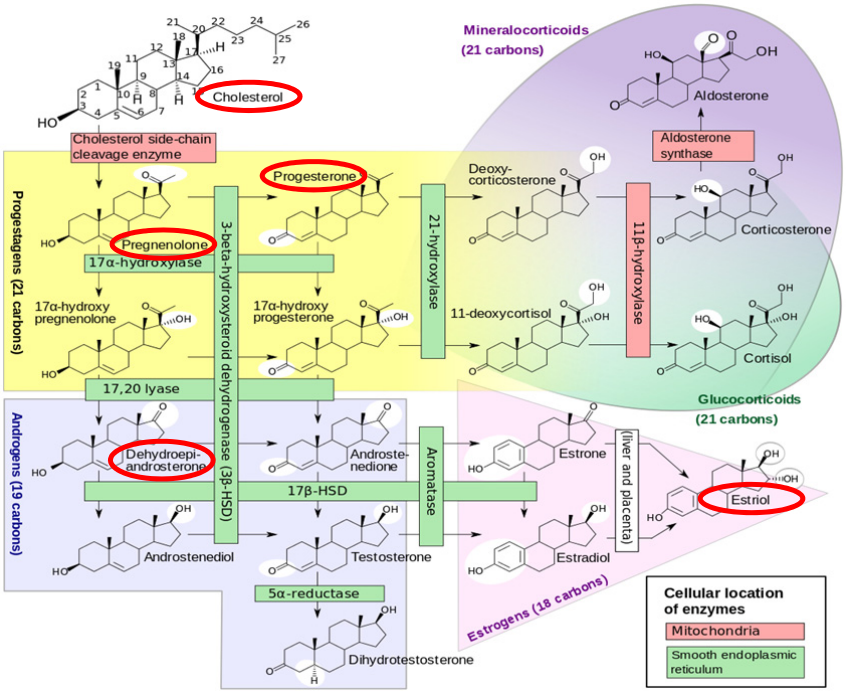

Figure 1. *Human steroidogenesis with major classes of steroid hormones and enzymatic pathways. Discussed hormones or their precursors are indicated in a red oval. (Figure by Häggström et al. (2014) [1])*

Menopause

Aging of women is associated with a decline in granulosa cells of the ovary, and consequently a decline of several steroid hormone levels including estrogen and progesterone. The decline in hormone levels disrupts the hypothalamic pituitary ovarian axis. As a result, deleterious effects on several organ systems occur, and irregular menstrual cycles follow. Menopause is the permanent cessation of menses for 12 months resulting from estrogen deficiency. The median age of menopause is 51 [2, 7, 8].

Hormone replacement therapy (HRT)

Menopausal women may experience hot flashes, vaginal dryness, mood changes, compromised cognition, and sexual problems (see Table 2). Hormone replacement therapy (HRT) is applied to women with hormones that are lost during the menopausal transition. Conventional HRT prescribed by a physician includes an estrogen and a progesterone component to mimic hormones created by the human ovary. As prolonged use of a high dose of estrogen alone will cause the endometrial lining to grow, woman indicated for HRT must be prescribed a progestagen with estrogen to protect the uterus from endometrial hyperplasia or malignancy [9]. In addition, progesterone has been commercially available for over 70 years to alleviate hot flashes and to reduce breast epithelial cell proliferation. Urogenital symptoms may be treated with estrogens only [10]. In the Netherlands, no

Table 2*. Health effects of menopause on different tissues/organs*

Organ	Effects
Vulva	Atrophy, pruritus vulvae
Vagina	Dryness, dyspareunia, vaginitis
Skin	Atrophy, dryness, pruritus; loss of elasticity, increased laxity, and fragility
Bones	Osteoporosis
Neuroendocrine system	Hot flashes, flushing, psychologic disturbances
Genitourinary system	Urethritis; urinary changes: urgency, frequency, or stress incontinence; bladder/uterine prolapse

Table by Hall and Philips (2005) [2]

dermal hormone creams containing progesterone, estriol, DHEA or pregnenolone are on the market as pharmaceutical products. However, there are dermal pharmaceutical products containing other hormones on the market in the Netherlands, such as testosterone (gel) and estradiol (as patches or as a spray).

HRT poses risks as well as benefits. In particular, an increased risk of breast cancer and cardiovascular disease as well as an increased risk of endometrial cancer, stroke, blood clots, ovarian cancer, and gallbladder disease has been associated with hormone therapies [11-13]. Estrogens and progestagens may be oral administered via a tablet or capsule, dermal via a cream, patch or subdermal pellets, or vaginal via a gel, cream or ovule. Dermal administration bypasses the first-pass hepatic metabolism resulting in lower doses being needed to achieve similar plasma concentrations. However, poor absorption of the active ingredients to the system is a known problem in transdermal products. In addition to low plasma levels, absorption of the hormones by the skin can result in high hormone levels locally, with corresponding possible side effects (e.g. in the case of DHEA, local carcinogenic effects can occur due to local conversion of DHEA into androgens and estrogens [11, 13]). Vaginal administration also bypasses the first-pass hepatic metabolism., This route of administration is often intentionally chosen to derive but with this application often local high hormone levels are intended

Over-the-counter creams containing hormones

Self-medication empowers patients to treat short-term physical discomfort which they consider not requiring the consultation of a physician. Women experiencing vasomotor symptoms (hot flashes and night sweats) may consider the use of over-the-counter products, which are promoted as aids in self-managing the symptoms of menopause. Web shops sell creams containing (low doses of) steroid hormones for use in menopause with claims such as "maintain a healthy balance naturally" and suggest that they may have a number of beneficial effects in postmenopausal women. Not only in protection of the endometrium, but also in the treatment of endometrial hyperplasia, relief of menopausal symptoms and even bone density.

Based on a sample of 27 over-the-counter products (see Annex I), creams may contain dehydroepiandrosterone (DHEA), estriol (E3), pregnenolone (P5) or progesterone (P4). An overview of selected hormones and recommended doses are shown in Table 3.
Warnings on the labels of the over-the-counter products include the following:

- Do not use when pregnant or breastfeeding/lactating or intend to become pregnant
- Use intended for adults
- Consult with your physician before using this product
- Do not exceed 2 oz (59 ml) of this product dermally per month
- Do not exceed the recommended daily dose

Sometimes a maximum number of consecutive days and a resume after a break of a specified number of days is indicated.
Comparing the maximum daily dermal application dose to the dose prescribed by a physician as

Table 3. *Overview of selected hormones and commonly applied doses*

Compound	**Other common names**	**CAS number**	**Number of examined products**	**Max dose dermal application of the examined creams** (mg/day)*	**Pharmaceutical products prescribed by physician** (max dose mg/day)**
Dehydroepiandrosterone (DHEA)	Prasterone	53-43-0	4	15	6.5
Estriol (E3)		50-27-1	3	1.5	8
Pregnenolone (P5)	PREG	145-13-1	1	15	-
Progesterone (P4)	-	57-83-0	13***	132	400
Wild Yam	-	-	5***	-	-
Phytoestrogen	-	-	1	-	-

**Dose is based on information provided on labels of hormone containing dermal creams (see Annex I)*
***Highest described dosage of available pharmaceutical products in the Netherlands, oral or vaginal intake, information is based on in the Dutch Pharmaceutical Products Data Bank (CBG geneesmiddeleninformatiebank, consulted at 19-03-2019) [14-16]*
****One product contains both progesterone and wild yam*

HRT (Table 3), it appears that the dose used for prescribed HRT (except for pregnenolone, as there are no pharmaceutical products with pregnenolone on the market in the Netherlands) is sometimes lower than the dose advised on the label of the creams for dermal application. It should be noted that HRT is administered either orally or vaginally which may result in a more efficient (systemic) absorption of the active component compared to dermal application.

Natural products

One product contains phytoestrogen, which is a plant-derived xenoestrogen [17]. The structure of phytoestrogen is similar to that of estradiol and it also has abilities to cause estrogenic effects. Four of the selected hormone creams are described as "Wild Yam" creams and have no declared concentration of a hormone. Several skin cream preparations based on 'natural ingredients' are marketed as supportive products during menopause. These creams may contain extracts of the Mexican wild yam as a source of progesterone/estrogen. The Mexican yam root contains the plant steroid diosgenin, which can (in a laboratory setting) be converted into estrogens. It is, however, unlikely that the human skin can absorb and subsequently convert diosgenin into biological active steroid hormones. Moreover, we did not find studies suggesting that dermal application of Mexican wild yam extracts results in beneficial effects in relation to reduce menopause-related symptoms [18, 19].

Some Mexican wild yam containing creams also provide black cohosh, a species of flowering plant containing estrogen-like compounds or other natural products. Other natural alternative therapies are based on (oral dietary) intake of phytoestrogens which are structurally similar to estradiol and often found in nuts, oilseeds and soy products. However, positive effects on menopause-related symptoms are not sufficient or proven. Furthermore, the (anti)estrogenic properties of phytoestrogens after oral application have raised concerns since they might act as endocrine disruptors, indicating a potential to cause adverse health effects [17, 20].

Combination of hormones

In one of the selected hormone creams, both progesterone and DHEA were detected. This was in contrast with the label of the cream, which declared progesterone only. It is, however, outside the scope of this risk assessment to issue the safety risks of hormone creams containing ingredients that are not declared on the label.

Evaluation of hormones present in selected creams

Dehydroepiandrosterone (DHEA)

Introduction

DHEA is a precursor steroid that is inactive, but is converted to active estrogens and androgens (see Figure 1). The DHEA creams examined have a recommended daily dose of 10 or 15 mg (Table 3). One of the selected dermal creams is indicated for men as a "boosting complex solution designed specifically for men's need". The desired effect, however, is unclear.
In the Netherlands, there is only one pharmaceutical product containing DHEA on the market, Intrarosa, an ovule containing 6.5 mg DHEA, (to be taken daily), which is indicated for the treatment of vulvar and vaginal atrophy in postmenopausal women [14].
DHEA is sold without a prescription as a dietary supplement (oral tablets up to 100 mg/day), which are promoted to prevent aging and obesity, increase muscle mass, improve overall well-being and strengthen the immune system [21]. It is outside the scope of this report to include these supplements in the current risk analysis.

Transdermal absorption

It has been proposed that treatment of postmenopausal women with DHEA will result in androgenic effects and hence improve libido and well-being via its conversion to testosterone, and in estrogenic effects resulting in improvements in menopausal vasomotor symptoms [22]. DHEA has been administered orally and parenterally, either by the transdermal or vaginal route. Percutaneous administration avoids first-pass metabolism in the liver, and closely mimics endogenous DHEA secretion and metabolism [23]. When administered to postmenopausal women, the serum levels of DHEA, androgens and estrogens increase, although it was shown that DHEA is mainly transformed to androgens rather than estrogens [24]. In the study by Labrie *et al.* (2007), it is shown that during chronic treatment with DHEA by cream or gel twice daily on the skin, the serum concentration of all the measured steroids rapidly reaches a plateau with no detectable change in the serum concentration of any of the steroids measured [24]. However, in another study, from 24 h after first administration of 30 mg DHEA percutaneously, the concentration of all steroids remain at the same level, thus showing that daily application of DHEA on the skin maintains constant serum levels of DHEA and all its metabolites [25]. In several studies it is shown that DHEA is metabolized into testosterone in the skin [25]. Studies indicate that there is a concern for local carcinogenic effects due to the locally conversion of DHEA into androgens and estrogens [11, 13].

Medical benefits

Although DHEA levels decline with age, it circulates in sufficient concentrations in older individuals to provide an adequate concentration of precursor hormone for the production of its estrogenic and androgenic metabolites throughout life. Most randomized controlled trials have not demonstrated a beneficial effect of DHEA therapy on well-being in postmenopausal women [22]. However, DHEA supplementation has been shown to have modest effects on bone density, and other studies suggest some benefits on the bone, skin, vagina, glucose and insulin metabolism [24]. In addition, DHEA replacement could play a role in prevention and treatment of the metabolic syndrome associated with abdominal obesity in both men and women [21]. In a study by Morales *et al.* (1998) it was shown that using a daily oral dose of 100 mg DHEA for six months resulted in elevation of circulating DHEA in men and women [26]. Only in two subjects (out of 19) minor side effects were reported.

Relevant pharmaceutical product(s)

The dermal creams examined had a recommended maximum daily dose of 15 mg. According to the study of Labrie *et al.* (2007), this dose corresponds in postmenopausal women to an increase in serum levels to 3-5 ng/mL [24]. This is similar to the maximum serum level of 4.4 ng/mL that is induced by Intrarosa (ovule 6.5 mg) on day 7 [14]. The side effects, contra-indications and interactions with other pharmaceutical products that are mentioned in the product characteristics file of Intrarosa (see Annex II) are therefore possibly a good indication for the application of the dermal cream. Of course, effects and interactions on the application site, mentioned in the product characteristics file of Intrarosa, are not taken into account, as these are different for dermal creams than for an ovule. Unfortunately, information about the effects and interactions on the application site of dermal creams containing DHEA could not be found in the literature.

Side effects

It is important to note that Intrarosa is only prescribed in a situation where the postmenopausal symptoms have a negative influence on the quality of life [14]. In all cases, it is stated that the benefits and risks must be carefully assessed by a physician at least every 6 months, and that Intrarosa should only be continued as long as the benefits outweigh the risks. In addition, it is mentioned that regular monitoring is recommended during treatment.

Side effects of Intrarosa include the development of cervical and uterine polyps, and weight fluctuations (see Annex II) [14].

Contra-indications

Intrarosa is contra-indicated for patients with breast cancer and estrogen-sensitive malignant tumors, liver disease, thrombophilic disorders, venous and arterial thromboembolic disorders, and porphyria [14]. Treatment with Intrarosa should also be discontinued in the following situations: jaundice or deterioration of liver functions, significantly increased blood pressure, new occurrence of migraine headache, and pregnancy. Furthermore, patients with a history of endometrial hyperplasia, leiomyoma or endometriosis, hypertension, diabetes mellitus, cholelithiasis, migraine or (severe) headache, epilepsy and asthma should be carefully monitored.
Intrarosa is not indicated for use in premenopausal women/fertile women, including women during breastfeeding.

Interactions with other pharmaceutical products

The product characteristics file of Intrarosa states that concomitant use with systemic HRT (estrogen only or combinations of estrogen/progestagen, or androgen treatment) or vaginal estrogens has not been investigated and is therefore not recommended [14]. No further information is available about interactions of DHEA with other pharmaceutical products.
The effect of concomitant dermal products on the absorption of DHEA has not been assessed.

Overdose

In case of vaginal overdose, a vaginal douche is recommended in the product characteristics file of Intrarosa [14]. This indicates a low acute toxicity.
It should be mentioned that DHEA is without a prescription sold as a dietary supplement (oral tablets containing up to 100 mg/day DHEA) [21]. Simultaneous use of both products can lead to a higher risk of overdosing. It is outside the scope of this report to include these supplements in the current risk analysis.

Summary and conclusion on DHEA

- Based on the available information, the dermal application of DHEA cream (15 mg/day) results in about the same serum levels compared to the use of Intrarosa (ovule). Other studies show absorption and metabolism of DHEA in the skin, giving concern for local carcinogenic effects of the dermal creams.
- Similar side effects can therefore be expected, which include the development of cervical and uterine polyps, and body weight fluctuations.
- Contra-indications indicate that patients with amongst others breast cancer, malignant tumors, and history of endometrial hyperplasia are at high risk. In addition, special care is necessary for a large group of people, with e.g. hypertension, diabetes, migraine, and epilepsy.
- Information on interaction of DHEA with other pharmaceutical products is limited.
- In case of misuse (overdosing) of Intrarosa, only a vaginal douche is advised, indicating low acute toxic effects. As dietary supplement, oral tablets containing up to 100 mg/day DHEA are available. Simultaneous use of both products can lead to a higher risk of overdosing. Possible additional use of dietary supplements is not included in this risk analysis.
- The contradictory results in changes in serum concentrations (and subsequent clinical effects) following dermal application of DHEA hampers a firm conclusion on potential risks to public health and in particular (pre- and/or post-) menopausal women. Based on the data available on pharmaceutical products containing DHEA, it can be concluded that the use of dermal creams containing DHEA may be a serious risk for patients with hormone dependent cancers. Also other vulnerable groups which may pose a risk are identified which include diabetics, people with severe hepatic impairment, and people with hypertension.

Estriol (E3)

Introduction

Estriol is the final metabolite of the estrogen synthesis, which cannot be converted back into estrone or estradiol.
For the three estriol-containing dermal creams examined, the recommended daily dose of estriol is 1.5 mg (Table 3). Next to dermal creams for postmenopausal women, in the US, estriol may also be used in several personal care products indicated as "youth enhancer" [27].
In the Netherlands, estriol is in several pharmaceutical products on the market, namely Blissel 50 µg/g gel for vaginal use, DR. KADE 0.03 mg ovules, Synapause-E3 0.5 mg ovules, Synapause-E3 1 mg tablets and Synapause 1 mg/g cream for vaginal use.

Transdermal absorption

After oral administration, estriol is readily absorbed and metabolized in the liver. Only 1–2% of the administered dose may reach the circulation in an unchanged active form [28]. Therefore, the daily dose of estriol in oral products is high, compared to the dose in vaginal products. Oral administration of 8 mg estriol gives serum levels of 75-220 pg/mL. Surprisingly, in the product characteristics file of the pharmaceutical product Synapause-E3 1-2 mg oral tablets, it is mentioned that the C_{max} of the plasma concentration is around 200 ng/mL, which is three orders of magnitude higher.

Following vaginal application (circumventing the first-pass metabolism through the liver), about 20% of the dose reaches the circulation in an unchanged form [28]. Pharmaceutical products for vaginal applications have dose levels than oral products, ranging from 30 µg per day to 0.5 mg per day. The highest plasma levels resulted from vaginal exposure are around 100 pg/mL. Unfortunately, no information is available on absorption of dermal creams and corresponding plasma or serum levels. Kainz *et al.* (1993) stated that estriol concentrations (following dermal application of 1 g 0.3% estriol/day for three months) used in their study do not result in systemic effects [29].

Medical benefits

Estriol (0.5 mg/day vaginal cream) is a preferred medication in the treatment of atrophy of the lower urogenital tract as estriol binds to the endometrial estrogen receptor to exert a vaginotropic effect [30]. The binding is weak and the duration of the binding is short. Since induction of endometrial mitosis (which may result in endometrial cancer) requires long-term interaction, estriol does - in contrast to other estrogens - not cause endometrial proliferation. Estriol (2-4 mg/day) is also used to treat hot flashes and may improve bone density [31].

It is known that estrogen alone will cause the endometrial lining to grow, and therefore woman with an intact uterus that are indicated for HRT must be prescribed a progestagen with estrogen to protect the uterus from endometrial hyperplasia or malignancy [9]. In the product characteristics file of Synapause E3 1-2 mg tablets, it is indeed mentioned that the treatment of women with a intact uterus should be combined with a progestagen [32]. However, in the product characteristics file of Estriol DR. KADE, it is mentioned that for estrogen products for vaginal application of which the systemic exposure to the estrogen is very low, it is not recommended to add a progestagen [33]. The systemic exposure to estrogen is after application of dermal creams is unknown, and therefore it is unclear if a dermal cream with estriol should be combined with a progestagen.

Relevant pharmaceutical product(s)

As no information is available about transdermal absorption and corresponding plasma or serum levels of dermal creams, it is unclear whether the absorption of dermal creams is comparable to the absorption of estriol via vaginal creams or ovules. However, as oral products certainly are absorbed differently, side effects and contra-indications of pharmaceutical products with a vaginal application are possibly the best indication for those of the dermal creams. Transdermal creams examined have a highest daily dose of 1.5 mg. These are compared with the vaginal cream Synapause-E3 with a recommended daily dose of 0.5 mg estriol which is the most comparable [16].

Side effects

In scientific literature, little information about side effects and contra-indications of estriol therapy is available. The use of estriol in high doses may have a stimulatory effect on both breast and

endometrial tissue [6, 27]. Takahashi *et al.* (2000) mention that oral estrogen (2 mg/day) relieves menopause symptoms without side effects, while a daily dose of 8 mg (oral) induce side effects such as nausea and mastalgia [34].

Side effects of Synapause-E3 include fluid retention, nausea, sensitive breasts, chest pain and flu-like symptoms (see Annex III) [16].

Contra-indications

Synapause-E3 is contra-indicated for patients with breast cancer and malignant estrogen-sensitive tumors, liver disease, thrombophilic disorders, venous and arterial thromboembolic disorders, and porphyria [16]. Treatment should also be discontinued in the following situations: jaundice or deterioration of liver functions; significantly increased blood pressure; new occurrence of migraine headache; pregnancy. Furthermore, patients with a history of endometrial hyperplasia, leiomyoma or endometriosis, hypertension, diabetes mellitus, cholelithiasis, migraine or (severe) headache, epilepsy and asthma should not use Synapause-E3. Synapause-E3 is not indicated for use in premenopausal women, including breastfeeding women should be carefully monitored.
Although estriol appears to be much safer than estrone or estradiol, it is suggested that continuous use in high doses may have a stimulatory effect on both breast and endometrial tissue [6, 27]. Therefore, it is generally advised to be used with caution in patients at risk for hormone-dependent cancers.

Interactions with other pharmaceutical products

Pharmaceutical products known to induce enzymes which are involved in drug metabolism, in particular in the hepatic cytochrome P450 3A4 mediated metabolism, such as anti-epileptics, antibacterial/antiviral agents as well as herbal medicines such as St. John's wort, may increase the metabolism and thereby decrease the bioavailability of estrogens and progestagens like estriol [35]. The pharmaceutical products Ritonavir and Nelfinavir, although known as strong inhibitors of cytochrome P450 3A4 mediated metabolism, have an inducing effect on the metabolism of estrogens and progestagens when used with steroid hormones. Clinically, an increased metabolism of estrogens and progestagens can lead to a reduction in efficacy and changes in bleeding pattern. The effect of concomitant dermal products on the exposure of estriol has not been assessed.

Overdose

The product characteristics files of pharmaceutical products of Blissel 50 µg/g gel for vaginal application and Synapause E3 1 mg/g cream for vaginal application containing estriol state that in the case of an accidentally ingested high dose, symptoms that may occur are nausea, vomiting and vaginal bleeding in females [35, 36]. There is no known specific antidote. If necessary, a symptomatic treatment should be instituted.
As estriol is a final metabolite, this may result in an increased risk on overdose.

Summary and conclusion on estriol

- No information on the absorption of estriol from dermal creams (1.5 mg/day) and corresponding skin, plasma or serum levels is available. Following oral exposure, large variations in serum levels are shown.
- Based on the information on Synapause-E3 (vaginal cream), side effects may include fluid retention, nausea, sensitive breasts, chest pain and flu-like symptoms.
- Metabolism may increase by concurrent use of pharmaceutical products inducing cytochrome P450 mediated metabolism.
- Contra-indications point out a high risk for patients with amongst others breast cancer, malignant tumors, and history of endometrial hyperplasia. In addition, special care is necessary for a large group of people, with e.g. hypertension, diabetes, migraine, and epilepsy.
- In case of an overdose, symptoms that may occur are nausea, vomiting and vaginal bleeding in females. There is no known treatment in case of an overdose, if necessary; a symptomatic treatment should be instituted.
- The lack of data on dermal absorption of estriol hampers a firm conclusion on potential risks using dermal creams containing estriol by (pre- and/or post-) menopausal women. However, based on the data available on pharmaceutical products containing estriol, it can be concluded that the use of dermal creams containing estriol may be a serious risk for patients with hormone dependent cancers. Also other vulnerable groups which may pose a risk are identified which include diabetics and people with hypertension.

Pregnenolone (P5)

Introduction

Pregnenolone serves as the major precursor for all steroid hormones (see Figure 1), although it also possesses intrinsic physiological activity as neurosteroids. Pregnenolone is produced *in situ* in the brain. In the 1940s, pregnenolone was first used in clinical practice as an anti-inflammatory agent. At the same time, cortisone with its superior anti-inflammatory effects was used for the first time, wherefore the clinical development of pregnenolone was not pursued.
Due to the key function of pregnenolone in the synthesis of other hormones, it is sometimes advertised as to boost the production of other hormones and may make people feel more energetic and younger. However, there is no clear scientific evidence that pregnenolone is effective for this purpose [37].
The examined dermal creams containing pregnenolone had a recommended daily dose of 15 mg (Table 3).
No pharmaceutical products containing pregnenolone as active ingredient are on the market. Pregnenolone is without a prescription also sold as a dietary supplement (oral products containing up to 150 mg/day pregnenolone). It is outside the scope of this report to include these supplements in the current risk analysis.

Transdermal absorption

Following transdermal administration of 30 mg pregnenolone for six days (to healthy men), no effects on the investigated steroids was observed [37], suggesting a very limited dermal absorption and/or skin metabolism. In men orally exposed to 50 mg pregnenolone, significant increased urinary levels of progesterone metabolites were found, while only minimal or negligible effects on urinary levels of DHEA, testosterone and metabolites could be observed [37, 38]. The data of the creams are contradictory, as one study showed no effects on the investigated steroids, but another study showed increased urinary levels. Unfortunately, no further information of transdermal administration is available. A single oral dose of 400 mg pregnenolone in healthy male volunteers resulted in a threefold elevation in serum levels of pregnenolone (up to 12 nmol/L) [39]. After intranasal administration, the bioavailability of pregnenolone was shown to be low (around 23%) [40].

Medical benefits

Treatment with pregnenolone may have beneficial effects on several neurologic processes in the brain related to anxiety, depression and psychosis-related disorders [39-41]. No studies on beneficial effects using dermal pregnenolone cream are available.

Relevant pharmaceutical product(s)

In the Netherlands, the use of pregnenolone is at this moment not available in pharmaceutical products.

Side effects

Information on side effects of the use of prenenolone is very limited. In a study by Brunner *et al.* (1951), (dermal) side effects such as seborrhoeic dermatitis were observed following oral administration of 100-150 mg/day pregnenolone during >14 days [4].

Contra-indication

No information available.

Interactions with other pharmaceutical products

In general it is mentioned that in case of large excess of endogenous or exogenous (sex) steroids, it is supposed that pregnenolone would help in maintaining an equilibration of steroidal environment by furnishing substances along other paths [42].

Overdose

No information available.
It should be mentioned that pregnenolone is without a prescription sold as well as a dietary supplement (oral products containing up to 150 mg/day pregnenolone) [21]. Using both the oral supplements and the dermal cream could lead to a higher risk of overdosing. It is outside the scope of this report to include these supplements in the current risk analysis.

Summary and conclusion on pregnenolone

- The little data available about the dermal absorption of pregnenolone is contradictory.
- No pharmaceutical products contain pregnenolone as active ingredient.
- No information on possible side effects is available.
- No information on contra-indications is available.
- No information on overdosing is available.
- Only little information is available about pregnenolone products, and therefore the eventual risk could not be extensively substantiated.

Progesterone (P4)

Introduction

Progesterone (P4) is the most important progestagen in the human body. The examined dermal creams containing progesterone had a recommended daily dose of 132 mg (Table 3).
In the Netherlands, progesterone is in several pharmaceutical products on the market. For oral applications, progesterone is available in Utrogestan 100 mg capsules and Besins 100 mg or 200 mg capsules. For vaginal applications, progesterone is available in Crinone 80 mg/g gel, Lutinus 100 mg tablets and Cyclogest 400 mg ovules.

Transdermal absorption

Progesterone levels observed during the luteal phase of the menstrual cycle are >30 nmol/L (serum) and >15 nmol/L (plasma) [43-45]. Postmenopausal progesterone serum levels are usually lower (0.05-0.33 nmol/L) [46], which can be increased by therapy using progesterone.
Transdermal absorption of progesterone appears to be poor, although the data is contradictory.

In some studies, a small increase in serum and plasma progesterone levels (up to <10 nmol/L for serum and 3.5 nmol/L for plasma) has been observed in postmenopausal women following dermal administration of 40 mg/g progesterone [44, 47-51]). In the study by Carey *et al.* (2000), in which 24 healthy postmenopausal women were dermally exposed to progesterone (40 mg daily for 42 days), an increase of the mean serum progesterone level up to 5.3 nmol/L is observed [47]. The maximum dose of dermal application indicated by information on labels is 132 mg/day (see Table 3), which would possibly results in higher serum levels than in the mentioned studies.

Despite the low serum progesterone levels achieved following dermal exposure, salivary progesterone levels are high (up to 80 nmol/L), indicating that progesterone levels in serum do not necessarily reflect those in tissues [49, 52]). Furthermore, the study by Du *et al.* (2013) showed that progesterone was also measurable in capillary blood (fingertip). Therefore, it can be concluded that progesterone levels in saliva and capillary blood may be a 10- and 100-fold greater, respectively, than levels found in serum or plasma [53]. This may be due to the fact that during the process of after skin-absorption, the lipophilic ingredients of creams, including progesterone, may have a preference for saturating the fatty layer below the dermis which is followed by a rapid uptake by red blood cells [45].

In one study, it was shown that whole blood progesterone levels (as opposed to mentioned serum concentrations) following daily dermal application of 40 mg progesterone twice on healthy postmenopausal women being roughly equivalent to the prescription of 200 mg oral dosage of progesterone daily [54]. 200 mg oral dosage of progesterone is a typical pharmaceutical dosage. Furthermore, it is known that orally administered progesterone undergoes a large first-pass effect.

Unfortunately, no information is available about hormone levels in the skin after application of the dermal progesterone creams.

Medical benefits

Several studies conclude that the measured serum levels achieved with progesterone creams are too low to have a secretory (protecting) effect on the endometrium (below the luteal-phase range of 32-95 nmol/L) or another clinical response in (post)menopausal women [45, 55, 56]. While several studies investigated the skin absorption of progesterone, only few studies also evaluated clinical parameters. In the study by Leonetti *et al.* (1999) in which postmenopausal women used 20 mg transdermal progesterone daily for 12 months, improvement or disappearance of vasomotor symptoms have been observed [57]. In another study with the same dose for six months, improved physical and emotional effects were observed in postmenopausal women [58]. In

contrast, another study showed no changes in clinical parameters such as vasomotor symptoms, moods, sexual enjoyment or quality of life after an exposure duration of 12 weeks to 32 mg progesterone [44].

Relevant pharmaceutical product(s)
The above mentioned measured serum values in postmenopausal women following dermal application of progesterone are lower compared to (therapeutically relevant) serum levels following (prescribed) vaginally delivery with an ovule of 400 mg (59 nmol/mL) [59]. Also, other pharmaceutical products containing progesterone are available in the Netherlands, but unfortunately, no information on serum levels after use is found. Product information of Crinone 80 mg/g gel for vaginal use, the product with the lowest concentration of progesterone after a daily dosage of 90 mg, is described below. This information is restricted to the general undesirable effects, which are probably caused by progesterone in the system (undesirable effects at the application site are not mentioned).This product gives the best indication available for the side effects and contra-indications of the dermal creams.

Side effects
Side effects of Crinone include hypersensitivity reactions (such as generalized itchy skin rash), sleepiness, headache, abdominal cramps, breast sensitivity and intermenstrual bleeding (see Annex IV) [15]. Gynecological checks must be carried out prior to and regularly during treatment with this pharmaceutical product. Since Crinone can cause fatigue, it is mentioned in the products characteristics file that caution is advised when driving motor vehicles and operating machines [15].

Contra-indication
Crinone is contra-indicated for patients with known or suspected malignancy of the breast of genitalia, thrombophlebitis, thromboembolic disorders, cerebral apoplexy and porphyria. Patients with diabetes, epilepsy, migraine, asthma, cardiac and renal impairment, severe hepatic impairment or a history of psychological depression should be carefully monitored. Furthermore, the product is not indicated during pregnancy and not recommended while breastfeeding. The product is indicated as part of an assisted reproductive technology procedure in fertile women.

Interactions with other pharmaceutical products
Since there was no information on the interactions of Crinone with other pharmaceutical products in the product characteristics file of Crinone, files of other pharmaceutical products were consulted. Pharmaceutical products known to induce the hepatic cytochrome P450 3A4 mediated metabolism (such as barbiturates, anti-epileptics (phenytoin, carbamazepine), rifampicin, phenylbutazone, spironolactone, griseofulvin, certain anticiotics (ampicillins, tetracyclines) as well as herbal medicines such as St. John's wort) may increase the elimination rate and thereby decrease the bioavailability of progesterone [59-61]. Ketoconazole and other cytochrome P450 3A4 inhibitors may increase the bioavailability of progesterone [60-62]. Although the indications are limited, it is considered possible that activated charcoal and griseofulvin could reduce the effectiveness of progesterone products. Conversely, progesterone may enhance the therapeutic, pharmacological, or toxicological effects of cyclosporine, theophylline, and troleandomycin [60]. Progesterone can reduce glucose tolerance and thus increase insulin resistance and resistance to all other antidiabetics that are administered to patients with diabetes mellitus [62].
The effect of concomitant dermal products on the exposure of progesterone has not been assessed.

Overdose
In general, the toxicity of progesterone is low and adverse effects of progesterone are very mild. However, in case of special sensitivity to the active substance or concomitantly excessive low levels of estradiol in the blood, woman using prescribed progesterone may be at risk when the dose is too high due to persistence or recurrence of unstable secretion of endogenous progesterone. Based on product characteristics files of pharmaceutical products (i.e. conventional HRT prescribed by a physician), an overdose of progesterone can cause drowsiness and (transient) dizziness [60-62]. This might particularly occur concurrently with hypoestrogenism as well as nausea, vomiting, euphoria and dysmenorrhea [59, 60, 62]. In one file it has been mentioned that side effects are usually signs of an overdose [62]. When an overdose has occurred, treatment with the products must be stopped or the dose must be lowered. No treatment of the progesterone overdose is necessary, but it is recommended to apply appropriate symptomatic and supportive care.

In case of an overdose in young children who swallowed several capsules at the same time (100 mg progesterone per capsule), no intoxication symptoms are expected [60]. Symptoms that could potentially occur include nausea, vomiting, drowsiness and dizziness. Specific treatment is not considered necessary but symptomatic treatment can be given.

Summary and conclusion on progesterone

- The data on transdermal absorption and following biological efficacy of progesterone is controversial. However, most studies show some increase of progesterone serum and plasma levels. It is expected that only sub-physiological levels of progesterone in premenopausal women can be achieved using progesterone dermal cream.
- Based on the information available on Crinone, side effects may include hypersensitivity reactions, sleepiness, headache, abdominal cramps, breast sensitivity and intermenstrual bleeding.
- Progesterone can increase insulin resistance in patients with diabetes mellitus, diabetics may thus be at risk using progesterone cream. Other vulnerable groups include people with suspected malignancy of the breast or genitalia, thrombotic disorders, severe hepatic impairment, and psychologic depression.
- In case of overdose, no intoxication symptoms are expected, indicating low acute toxic effects. An overdose of progesterone can cause symptoms such as drowsiness, dizziness, nausea, vomiting and euphoria. No treatment of the progesterone overdose is necessary, but it is recommended to apply appropriate symptomatic and supportive care.
- Due to the general lack of adverse effects at sub-physiological levels, no adverse effects are expected for postmenopausal women with intrinsic low progesterone levels. However, because of the uncertainty about the absorption of progesterone in dermal creams, giving low serum and plasma levels, but high levels in saliva and capillary blood, it is impossible to rule out any local or systemic risk.

Discussion

Introduction

Several factors influence the dermal absorption of active compounds in hormone creams. Information on dermal absorption of hormones in hormone containing creams is frequently lacking. The general lack of data hampers a full risk analysis on the use of the over-the-counter hormone containing creams. In this general discussion, some major issues influencing the dermal uptake of hormones and consequent internal exposure (i.e. serum levels), metabolism and systemically effects will be discussed.

As no information is available on the (side) effects, contra-indications, and overdose of dermal hormone creams, in this report, available information of pharmaceutical products containing hormones is used. In the Netherlands, no dermal creams containing one of the hormones (or a combination) are on the market as pharmaceutical products though other pharmaceutical products with hormones are available (on prescription):

- DHEA (maximum dose hormone cream 15 mg) is available as an ovule of 6.5 mg DHEA. DHEA is also sold as dietary supplement without description as (oral) capsules containing 15 up to 100 mg DHEA.
- Estriol (maximum dose hormone cream 1.5 mg) is available as vaginal cream (0.5 mg), ovule (0.03 or 0.05 mg), and oral tablets (4-8 mg).
- Progesterone (maximum dose hormone cream 132 mg) is available as a vaginal cream (90 mg), ovule (300-400 mg) or oral capsules (200-300 mg).
- No pharmaceutical products containing pregnenolone as active ingredient are available, however, dietary supplements without description are available (containing 5-100 mg pregnenolone).

Additionally, there are dietary supplements with both DHEA and pregnenolone available as well, however, information and data on dietary supplements are not included in this report.

Dermal application and absorption

To ensure adequate dermal absorption, creams often require application to several and/or large body parts as indicated, e.g. "Just massage a dime-size dollop cream into your skin. Try your wrists, arms, thighs and tummy." The creams must be allowed to dry before dressing to prevent transfer of the cream to clothing, and care must also be taken to avoid transfer to others. In one study, it was even stated that contact with the application site must be avoided for 1-2 hours [63, 64]. Also, the skin must be kept dry after application in order to maintain the absorption.
The low inherent skin permeability for hormones can be offset using appropriate absorption promoters. A variety of chemicals including ethanol, terpenes, essential oils and propylene glycol, can be used to enhance skin permeation [45, 65]. In addition to creams containing hormones, also gels and spray preparations have been developed which may result in an enhanced dermal uptake [63]. The transdermal permeation clearly depends on the vehicle present in the creams and should be taken into account in further risk analysis.
The description of suggested usage as mentioned on the label of the samples may allow different interpretations, which may result in variation in use including exceedance of the recommended dose. This concerns descriptions like "Fully depress the pump once or twice…", "Just massage a dime-size…", "Apply once or twice a day…".

Dermal administration bypasses the first-pass hepatic metabolism. As a consequence, lower doses need to be applied to achieve similar plasma concentrations. However, it is known that at least DHEA may already be metabolized in the skin [25], hampering a clear relationship between application and internal concentration (e.g. serum levels). Pregnenolone and progesterone may also be readily metabolized into other hormones. Estriol is the final metabolite of the estrogen synthesis. In addition, studies indicate that there might be a concern for local adverse effects due to the locally high concentration of hormones.
Several studies investigated the relationship between the administration (either oral or dermal) of hormones and serum levels in premenopausal and postmenopausal women. Due to large fluctuation and differences of endogenous hormones in pre- and postmenopausal women, study results differ largely, hampering comparison of studies and the different routes of application. In addition, due to the natural fluctuations and adequate metabolism into other hormones, it is difficult to assess whether possible changes in serum levels are a result of the use of a hormone cream and whether these changes may result in a clinical effects and medical benefits.

Clearly, several factors may influence the dermal absorption of hormones.

Side effects and contra-indications

In humans, levels of steroid hormones fluctuate over time in both men and women of all ages. In general, elevation of serum levels of steroid hormones will not immediately cause (acute) severe and/or irreversible adverse health effects. It is to be expected that via several pathways the equilibrium will be maintained. However, the metabolism of both estrogens and progesterons can be affected by other compounds (e.g. pharmaceutical products) which intervene the enzymatic pathways, e.g. drugs known to induce the hepatic cytochrome P450 system may increase the elimination rate and thereby decrease the bioavailability of the hormone.

No information is available on adverse effects and misuse or overdose of hormone creams. Information on the use of hormone creams and interaction with other pharmaceutical products is also lacking. Nevertheless, several vulnerable groups are identified:

- Women with (a history of) breast cancer and estrogen-sensitive malignant tumors
- Premenopausal women/fertile women, including pregnant women (and the unborn child) and during breastfeeding
- Diabetics, people with hypertension, migraine, thrombotic disorders, severe hepatic impairment and several other conditions
- People using pharmaceutical products known to induce enzymes which are involved in drug metabolism (in particular cytochrome P450)
- Children and adolescents

Other sources of exposure

Hormones mediate a major part of our essential physiological functions. Both endogenous and exogenous compounds and their metabolites are known to act through hormone receptors leading to regulation of endocrine function. In general, in case of large excess of (sex) steroids, the system will maintain an equilibrium of the steroidal environment by directing substances along other paths. However, these biological processes may be disturbed by endocrine disrupting compounds.

Irrespective of the (conscious) use of a hormone cream, exposure may also occur via other sources. For instance, personal care products (from outside the EU) can contain estrogens or xenoestrogens [66], and soy food may contain phytoestrogens which can act synergistically with estriol [6]. DHEA and pregnenolone are widely available as dietary supplements without a prescription [21]. For a full risk assessment, all possible other sources of exposure and substances which may interact with the endocrine system should be included.

Conclusion

Risk assessment of dermal creams containing hormones

In general, lack of data on (dermal absorption of) the discussed hormones and creams hamper a full risk assessment. Therefore, available information on serum/plasma levels and clinical effects of pharmaceutical products containing hormones is used in this risk assessment additionally to the information about the hormone creams.
The contradictory results in changes in serum concentrations following dermal application of DHEA, and the lack of data on dermal absorption of estriol hampers a firm conclusion on potential risks to (pre- and/or post-) menopausal women using DHEA or estriol containing creams. In the case of dermal creams containing pregnenolone or progesterone, limited absorption - and consequently low serum and plasma levels - is expected. However, due to uncertainties about absorption and lack on information, it is not possible to rule out any risk.

Based on the data available on pharmaceutical products, it can be concluded that the use of dermal creams containing DHEA or estriol may pose a risk for patients with hormone dependent cancers. Also other vulnerable groups are identified which include diabetics, people with severe hepatic impairment and people with hypertension.

Opinion on the questions

1. Is at exposure levels, based on the declared concentrations DHEA, estriol, pregnenolone, and progesterone and the prescribed use, a risk to public health to be expected?

It is generally known that levels of (steroid) hormones fluctuate in time naturally in (girls and) women to regulate the menstrual cycle and several other mechanisms. In boys and men, hormonal levels also vary over time. The human body has several mechanisms to cope with increased levels, and (a single) elevation of serum levels of steroid hormones will not immediately cause (acute) severe and/or irreversible adverse (toxic) health effects.
Several factors influence the dermal absorption of (active compounds in) hormone creams. Information on dermal absorption is frequently lacking, and for at least DHEA it is known that it may already be metabolized in the skin. No data is available on which serum levels will be achieved by using the creams.
The general lack of data hampers a full risk assessment and conclusion on potential risks to public health.

2. Given the use without medical supervision, can vulnerable groups of high-risk scenarios be identified?

As no information is available on adverse effects and overdose of hormone creams, available information of pharmaceutical products are used.
DHEA (Intrarosa), estriol (Synapause-E3) and progesterone (Crinone) containing pharmaceutical products are contra-indicated for patients with breast cancer and estrogen-sensitive malignant tumors, indicating that women suffering from these specific health issues may also be at risk for using hormone creams without medical supervision. The pharmaceutical products are not indicated for use in premenopausal women/fertile women, including pregnant women and during breastfeeding.
A decrease in glucose tolerance has been observed in a small number of patients treated with pharmaceutical products containing a combination of estrogen and progestin. For this reason, patients with diabetes can be identified as a possible vulnerable group. Also cases with a history of hypertension, cholelithiasis, migraine or (severe) headache, epilepsy, asthma, thrombotic disorders, severe hepatic impairment, and psychologic depression may (based on product characteristic files of pharmaceutical products containing the selected hormones) be identified as vulnerable group.
Based on the available product characteristic files of pharmaceutical products it can be mentioned that the metabolism of estrogens (and progestagens) may increase with concomitant use of substances known to induce enzymes, in particular specific cytochrome P450 enzymes, which are involved in drug metabolism. These substances include anti-epileptics (e.g., phenobarbital, phenytoin, carbamazepine) and antibacterial / antiviral agents (e.g. rifampicin, rifabutin, nevirapine and efavirenz). Based on this information, another vulnerable group can be identified (namely people using pharmaceutical products known to induce enzymes which are involved in drug metabolism).
Specific information on children and adolescents is not available, but may be identified as vulnerable group due their developing body and hormonal systems.

Despite the general lack on relevant data, several vulnerable groups are identified:

- Women with (a history of) breast cancer and estrogen-sensitive malignant tumors, because of an increased risk of these cancers
- Premenopausal women/fertile women, including pregnant women (and the unborn child) and during breastfeeding
- Diabetics, people with hypertension, migraine, thrombotic disorders, severe hepatic impairment and several other conditions
- People using pharmaceutical products known to induce enzymes which are involved in drug metabolism (in particular cytochrome P450)
- Children and adolescents

Elements included in the answers

1. Initially, the risk assessment can be performed using the highest declared concentrations of DHEA, estriol, pregnenolone, and progesterone. In case a risk is identified under these conditions, further refinement should be included.

See also the answer to question 1 above (Is at exposure levels, based on the declared concentrations DHEA, estriol, pregnenolone, and progesterone and the prescribed use, a risk to public health to be expected?).
As no risk assessment is performed, only (side) effects from exposure to the four hormones via creams are provided and discussed, no further refinement is included.

2. Besides the use by the intended target group (women with menopausal symptoms), possible vulnerable groups should be included. Groups for discussion are amongst others: pregnant women (unborn child), young children, adolescents, men, and specific health issues (e.g. hormone related (progesterone) breast cancer).

Several potential vulnerable groups are identified (see also the answer to question 2 above (Given the use without medical supervision, can vulnerable groups of high-risk scenarios be identified?)) which should be taken into account for complete risk assessment. These include pregnant women (and the unborn child), people with specific health problems, and (young) children and adolescents. One of the examined dermal creams containing DHEA is indicated for the use by men. Effects on men are not specifically included in this report.

3. Risks of overdosing (possibly encouraged in case of absence of desired effects) and the relevance of interaction with pharmaceutical products.

No information about overdose of hormone creams is available. Although based on available product characteristic files of pharmaceutical products, in general in case of (a single) overdose of one of the hormones, no short term reactions or mild intoxication symptoms are expected, and no treatment of the overdose is necessary.

Information on the use of hormone creams and interaction with other pharmaceutical products is also lacking. However, as mentioned above, based on the available product characteristic files of pharmaceutical products, it is known that certain pharmaceutical products induce enzymes which are involved in drug metabolism, and therefore people using specific pharmaceutical products are identified as vulnerable group to be included for further risk assessment.

The fact that the measured concentrations of hormones in the dermal creams are lower than the declared concentration gives reason to assess the risk of overdosing: when the desired effect is not achieved with the prescribed use, excessive use (with a higher exposure than the declared dose) by the consumer is a possible scenario.

Both DHEA and pregnenolone are available as dietary supplement. Concomitant use of cream and supplement may increase the risk on overdosing.

Uncertainties and considerations

Use of dermal creams containing hormones

The general lack of data hampers a full risk assessment and conclusion on potential risks of the use of hormone containing dermal creams to public health. Nevertheless, it can be concluded that:

- Clear medical benefits of dermal application of creams containing hormones are frequently disputed. Indeed, side effects may occur. For instance, prolonged exposure to estrogens stimulates the growth of endometrium, thus increasing the risk of endometrial hyperplasia.
- Dermal absorption depends on several factors, full details on the composition of the creams and their specific dermal absorption and effects (i.e. serum levels) is lacking. Additional studies on the dermal absorption of the mentioned hormones and safety of the use of hormone containing creams are required.

- Several possible vulnerable groups are indicated, including women with (breast) cancer and diabetics.
- Both DHEA and pregnenolone are also widely available as dietary supplements which may be an additional source of exposure that should be included in a risk analysis.
- One of the examined dermal creams containing DHEA is indicated for the use by men. This use is not included in the current report. Furthermore, substances, potentially influencing hormonal homeostatis, present in natural products like the "Mexican Wild Yam" creams are also not included in the risk assessment.

It can be questioned whether it is desirable that women suffering from (mild) menopause symptoms can 'treat' themselves by using hormone containing dermal creams. Information on possible contra-indications is not known or available to the consumer. In addition, it could be useful to inform women on the possible risks and/or unwanted effects among the use of over-the-counter available dermal creams containing hormones.

Recommendation Dutch College of General Practitioners (NHG)

In the NHG-Standaard M73 'De Overgang' ('The Menopause') of the Dutch College of General Practitioners (NHG), guidelines for diagnoses, (pharmaceutical product) treatment and education/information intended for the patient are defined [10]. The NHG-Standaard M73 recommends general practitioners (GPs) to inform their patients that it is not recommended to use natural or herbal products, supplements or therapies (including the in this report discusses hormone creams) to 'self-cure' menopause-related symptoms, as beneficial effects are not proved and they may cause serious side effects.
GPs could play a part in the communication to women suffering from (mild) menopause symptoms considering the use of over-the-counter available dermal creams containing hormones.

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Annex I Table NVWA

Annex I Available creams listed by NVWA

	Overzicht cremes met hormonen										
		Onderzoeksresultaten									
Volgnr	Monster-nummer	Progesteron mg/g	Estradiol mg/kg	DHEA (dehydroepi-androsterone) mg/g	Declaratie hormoon op etiket	(Maximale) dosering creme in gram op basis etiket per dag	(Maximale) dosering progesterone in mg per dag analyse resultaat	(Maximale) dosering DHEA in mg per dag analyse resultaat	(Maximale) dosering progesterone in mg per dag gehalte opgave etiket	(Maximale) dosering DHEA in mg per dag gehalte opgave etiket	(Maximale) dosering estriol in mg per dag gehalte opgave etiket
1	87258866	n.a.	n.a.	n.a.		2,6 g/dag (2 x pomp hoeveelheid daags)					
2	87258874	8,97	n.a.	n.a.	progesterone, 450 mg of usp progesterone per ounce (20 mg per 1/4 teaspoon)	2,6 g/dag (2 x dime-size hoeveelheid / 1/4 theelepel daags)	23 mg/dag		40 mg/dag		
3	87258882	n.a.	n.a.	n.a.		2,6 g/dag (2 x dime-size hoeveelheid daags)					
4	87258904	n.a.	n.a.	n.a.	estriol 18 mg of estriol per ounce (0,75 mg per 1/4 teaspoon)	2,6 g/dag (2 x dime-size hoeveelheid daags)					1,5 mg/dag
5	87258912	13,17	n.a.	n.a.	progesterone, 1 full pump dispence about 1.3 g of cream, providing 20 mg of progesterone	2,6 g/dag (2 x pomp hoeveelheid daags)	34 mg/dag		40 mg/dag		
6	87258939	n.a.	n.a.	6,1	dehydroepiandrosterone (DHEA). Each pump provides approximately 15 mg of DHEA	1,3 g/dag (1 x pomp hoeveelheid)		8 mg/dag		15 mg/dag	
7	87258947	n.a.	n.a.	n.a.	estriol. Approximately 750mcg per dose (= 750 ug per dose	2,6 g/dag (2 x pomp hoeveelheid) Betreft een pomp verpakking					1,5 mg/dag
8	87258955	9,44	n.a.	n.a.	progesterone. Each full press of the pump supplies 20 mg of progesterone.	1,3 g/dag (1 x pomp hoeveelheid daags)	12 mg/dag		20 mg/dag		
9	87258963	n.a.	n.a.	n.a.	pregnenolone (3B-hydroxypregn-5-en-20-one). Each pump provides approximately 15 mg of natural pregnenolone	1,3 g/dag (1 x pomp hoeveelheid daags)			15 mg pregnenolone/dag		
10	87258971	n.a.	n.a.	n.a.	Each full press of the pump provides approximately 0,75 mg of natural estriol. This estriol-care is formulated to contain 18 mg of estriol per ounce	2,6 g/dag (2 x pomp hoeveelheid daags) Betreft een pomp verpakking					1,5 mg/dag
11	87258998	10,94	n.a.	n.a.	progesterone. Each full press of the pump provides approximately 20 mg of progesterone. This progesterone cream is formulated to contain 480 mg of progesterone per ounce	2,6 g/dag (2 x pomp hoeveelheid) Betreft een pomp verpakking	28 mg/dag		40 mg/dag		
12	87259005	n.a.	n.a.	5,16	dehydroepiandrosterone (DHEA). Each full press of the pump provides approximately 10 mg of DHEA	1,3 g/dag (1 x pomp hoeveelheid daags)		7 mg/dag		10 mg/dag	

13	87259013	n.a.	n.a.	7,36	dehydroepiandrosterone (DHEA). Each full press of the pump provides approximately 15 mg of DHEA	1,3 g/dag (1 x pomp hoeveelheid daags)		10 mg/dag		10 mg/dag	
14	87259021	11,25	n.a.	n.a.	progesterone. Each full press of the pump provides approximately 20 mg of progesterone. This progesterone cream is formulated to contain 480 mg of progesterone per ounce	2,6 g/dag (2 x pomp hoeveelheid daags) Betreft een pomp verpakking	29 mg/dag		40 mg/dag		
15	87259048	n.a.	n.a.	7,88	dehydroepiandrosterone (DHEA). Each press of the pump provides approximately 15 mg of natural DHEA	1,3 g/dag (1 x pomp hoeveelheid daags)		10 mg/dag		15 mg/dag	
16	87259056	n.a.	n.a.	n.a.		2,6 g/dag (1/2 theelepel daags)					
17	87259064	n.a.	n.a.	n.a.		geen opgave, schatting 2,6 g/dag					
18	87259072	11,06	n.a.	n.a.	progesterone (10 mg per 1/8 teaspoon)	2,6 g/dag (1/4 theelepel 2 x daags)	28 mg/dag		40 mg/dag		
19	87259099	12,33	n.a.	n.a.	progesterone (10 mg per 1/8 teaspoon)	2,6 g/dag (1/4 theelepel 2 x daags)	32 mg/dag		40 mg/dag		
20	87259102	15,56	n.a.	n.a.	progesterone 2,4 % (= 24 mg/g)	2,6 g/dag (1/4 theelepel 2 x daags)	40 mg/dag		62 mg/dag		
21	87259129	14,14	n.a.	n.a.	progesterone, provides 580 mg of progesterone per 30 gram and 24 mg per 1/4 teaspoon	5,2 g/dag (1/2 theelepel 2 x daags)	74 mg/dag		96 mg/dag		
22	87259137	n.a.	n.a.	n.a.		1,7 g/dag (1/3 theelepel daags)					
23	87259145	n.a.	n.a.	n.a.		geen opgave, schatting 1,3 g/dag					
24	87259153	11,25	n.a.	n.a.	progesterone	2,6 g/dag (2 x dime-size hoeveelheid daags)	29 mg/dag				
25	87259161	13,7	n.a.	n.a.	progesterone usp from soy (500 mg per ounce)and 22 mg per 1.30 grams (approximatly 1/4 teaspoon)	5,2 g/dag (1/2 theelepel 2 x daags)	71 mg/dag		88 mg/dag		
26	87259188	1,59	n.a.	n.a.	progesterone (22 mg per 1/4 tsp.)	7,8 g/dag (3/4 theelepel 2 x daags)	12 mg/dag		132 mg/dag		
27	87210154	6,85	n.a.	4,19	progesterone 2,0 % = 20mg/g (opgave op bijsluiter)	1,3 g/dag (1 x daags)	9 mg/dag	5 mg/dag	26 mg/dag		
1/4 teaspoon is 1,3 g 1 full pump press is 1,3 g 1 dime-size dollop is 1,3 g											

Annex II DHEA

Parts of the product characteristics file of Intrarosa, 6,5 mg ovule [14].

Side effects

System Organ Class	**Common (≥1/100, <1/10)**	**Uncommon (≥1/1.000, <1/100)**
Reproductive system and breast disorders	Abnormal smear (mainly ASCUS or LSIL)	Cervical / uterine polyps Breast mass (benign)
Investigations	Weight fluctuations	

Side effects of combination-HST

- Higher risk of breast cancer
- Higher risk of venous thromboembolism
- Higher risk of ischemic cerebrovascular accident

Contra-indications

- Hypersensitivity to the active substance or to the excipient listed in the product
- Unexplained vaginal bleeding;
- Known, earlier or suspected breast cancer;
- Known or suspected estrogen-sensitive malignant tumors (eg endometrial cancer);
- Untreated endometrial hyperplasia;
- Acute liver disease or a history of liver disease, as long as the liver function values are not normalized;
- Previous or existing venous thromboembolism (deep vein thrombosis, pulmonary embolism);
- Known thrombophilic disorders (e.g. protein C, protein S or antithrombin deficiency, see section 4.4);
- active or recent, arterial thromboembolic disorder (eg, angina, myocardial infarction);
- Porphyria

Special warnings and precautions for use

For the treatment of postmenopausal symptoms, Intrarosa should only be started if the symptoms have a negative influence on the quality of life. In all cases, the benefits and risks must be carefully assessed at least every 6 months, and Intrarosa should only be continued as long as the benefits outweigh the risks after consultation of the patient with her doctor.

A full medical history (including family history) must be taken before starting treatment with Intrarosa. Physical examination (including gynecological and breast examination) should be performed on the basis of the history, the contra-indications and special warnings and precautions for use in accordance with the decision of her doctor. Regular monitoring is recommended during treatment. The frequency and nature of the controls are adjusted to the individual need for the woman. Women should be told what changes in their breasts they should report to their doctor or nurse (see below under "Breast Cancer"). Investigation, including smears and blood pressure measurements, should be performed in accordance with current screening practice, taking into account the medical need for the individual woman.

Conditions where control is required

Patients who have or have had one of the following conditions in the past and / or whose one of the following conditions worsened during pregnancy or prior hormonal treatment should be carefully monitored. It must be borne in mind that these disorders may recur or worsen during treatment with Intrarosa, this is especially true for:

- Leiomyoma (fibroids) or endometriosis;
- Risk factors for thromboembolic disorders (see below);

- Risk factors for estrogen-sensitive tumors, that is breast cancer in a first-degree family member;
- Hypertension;
- Liver disorders (e.g. liver adenoma);
- Diabetes mellitus with or without vascular symptoms;
- Cholelithiasis;
- Migraine or (severe) headache;
- Systemic lupus erythematosus;
- A history of endometrial hyperplasia (see below);
- Epilepsy;
- Asthma;
- Otosclerosis.

Reasons to immediately stop the treatment
Treatment should be discontinued if a contraindication is found and in the following situation:
- Jaundice or deterioration of liver functions;
- Significantly increased blood pressure;
- New occurrence of migraine headache;
- Pregnancy.

Fertility, pregnancy and lactation
Pregnancy
Intrarosa is not indicated for use in premenopausal women who may have children, including pregnant women. If the woman becomes pregnant during treatment with Intrarosa, treatment must be stopped immediately. There are no data from the use of Intrarosa in pregnant women. Animal reproduction toxicity studies have not been performed (see section 5.3). The potential risk in humans is unknown.

Breastfeeding
Intrarosa is not indicated during breastfeeding.

Fertility
Intrarosa is not indicated in fertile women.

Effects on ability to drive and use machines
Intrarosa has no influence on the ability to drive and use machines.

Interaction with other pharmaceutical products and other forms of interaction
Concomitant use with systemic hormonal replacement therapy (estrogen only or combination of estrogen / progestogen or androgen treatment) or vaginal estrogens has not been investigated and is therefore not recommended.

Overdose
In the event of an overdose, a vaginal shower is recommended.

Annex III Estriol

Parts of the product characteristics file of Synapause-E3 1mg/g, cream for vaginal application [16].

Side effects

System Organ Class	**Unknown**
Nutrition and metabolic disorders	Fluid retention
Gastrointestinal disorders	Nausea
Reproductive system and breast disorders	Sensitive breasts Chest pain Postmenopausal spotting Cervical discharge
General disorders and administration site conditions	Irritation at the application site Pruritus at the application site Flu-like symptoms

Other side effects reported that are associated with estrogen/progestogen treatment:

- Benign and malignant estrogen-dependent neoplasms, for example endometrial carcinoma.
- Gallbladder disorders
- Skin and subcutaneous tissue disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura
- Possible dementia over the age of 65 (see section 4.4)
- Risk of breast cancer
- Slightly increased risk of ovarian carcinoma
- Risk of venous thromboembolism
- Risk of coronary heart disease
- Risk of an ischemic cerebrovascular accident

Contra-indications

- Hypersensitivity to the active substance or to any of the excipients
- Presence or suspicion of breast cancer; history of breast cancer
- Presence or suspicion of malignant estrogen-sensitive tumors (e.g. endometrial carcinoma)
- Vaginal bleeding whose cause has not been established
- Untreated hyperplasia of the endometrium
- Past or presence of venous thromboembolism (deep vein thrombosis, pulmonary embolism)
- Presence of thrombophilic disorders (for example protein C, protein S or an antithrombin deficiency)
- Active or recently experienced arterial thromboembolic disorder (angina, myocardial infarction)
- Acute liver disease or history of liver disease, as long as the liver function values are not normalized
- Porphyria

Special warnings and precautions for use

For the treatment of symptoms of estrogen deficiency in postmenopausal women, treatment with HRT should only be started if these symptoms adversely affect quality of life. Periodically, at least annually, a careful assessment of the advantages and disadvantages of HRT should be made and treatment should only be continued if the benefits outweigh the disadvantages.

Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited. But due to the low absolute risk among young women, the balance of advantages and disadvantages may turn out to be more positive for these women than for older women.

Medical examination/follow-up

Before starting HRT or when use is resumed after an interruption, a full medical history (including family history) must be taken. Physical examination (including gynecological and breast examination) must be based on the history, the contra-indications and the warnings. Regular checks are recommended during the treatment period, the frequency and nature of which are adjusted individually. Women should be told which changes in their breasts they should consult

with their doctor or nurse immediately (see "Breast Cancer" below). Periodic examination of the breasts, including appropriate imaging techniques such as mammography, should be performed in accordance with the applicable guidelines for healthy women, taking into account the medical needs of the individual woman.

Conditions where control is required
If one of the following conditions is present, was present in the past and/or worsened during pregnancy or previous hormonal treatment, the patient must be additionally monitored. One should be aware that these conditions may recur or worsen during treatment with Synapause-E3, in particular:

- Leiomyoma (uterine fibromas) or endometriosis
- Risk factors for thromboembolic disorders (see "Venous thromboembolisms")
- Risk factors for estrogen sensitive tumors (breast cancer with first degree family member)
- Hypertension
- Liver disease (for example liver adenoma)
- Diabetes mellitus with or without vascular symptoms
- Cholelithiasis
- Migraine or (severe) headache
- Systemic lupus erythematosus
- A history of endometrial hyperplasia (see "Endometrial hyperplasia and carcinoma)
- Epilepsy
- Asthma
- Otosclerosis.

Reasons to immediately stop treatment
HRT should be discontinued immediately if a contraindication has been detected and in the following situations:

- Jaundice or deterioration of liver functions
- Significant rise in blood pressure
- The first occurrence of a migraine-like headache
- Pregnancy.

Fertility, pregnancy and lactation
Pregnancy
Synapause-E3 is not indicated for use during pregnancy. If pregnancy occurs during treatment with Synapause-E3, treatment must be terminated immediately. So far, the results of most epidemiological studies relevant to assessing the effects of unintended fetal exposure to estrogens do not indicate a teratogenic or fetotoxic risk.

Breastfeeding
Synapause-E3 is not indicated for use during the lactation period. It is known that estriol is excreted through breast milk and that it can reduce milk production.

Fertility
Synapause-E3 is only for use in postmenopausal women (with or without uterus).

Effects on ability to drive and use machines
Synapause-E3 has no known influence on the ability to drive and use machines.

Interaction with other pharmaceutical products and other forms of interaction
The metabolism of estrogens (and progestagens) may increase with concomitant use of substances known to induce enzymes, in particular cytochrome P450 enzymes, which are involved in drug metabolism. These substances include anti-epileptics (e.g., phenobarbital, phenytoin, carbamazepine) and antibacterial / antiviral agents (e.g., rifampicin, rifabutin, nevirapine, efavirenz). Ritonavir and nelfinavir, although known as strong inhibitors of metabolism, have an inducing effect when used with steroid hormones. The metabolism of estrogens and prostagens can also increase with phytotherapeutic preparations that contain St John's wort (Hypericum perforatum). Clinically, an increased metabolism of estrogens and progestagens can lead to a reduction in efficacy and changes in bleeding pattern.

Overdose
If large amounts are swallowed, possible symptoms could include nausea, vomiting, and

withdrawal bleeding in women and girls. A specific treatment is not known. If necessary, symptomatic treatment can be given.

Annex IV Progesterone

Parts of the product characteristics file of Crinone 80 mg/g gel for vaginal application [15].

Side effects
Immune system disorders
Not known: hypersensitivity reactions, such as generalized itchy skin rash.

Mental disorders
Common (≥1/100 to <1/10): sleepiness.

Gastrointestinal disorders
Common (≥1/100 to <1/10): abdominal cramps.

Reproductive system and breast disorders
Common (≥1/100 to <1/10): breast sensitivity
Rare (≥1/10.000 to <1/1.000) to very rare (<1/10.000): intermenstrual bleeding (spotting).

General disorders and administration site disorders
Common (≥1/100 to <1/10): headache.
Rare (≥1/10.000 to <1/1.000) to very rare (<1/10.000): vagina irritation and other minor reactions at the site of application.

During post-marketing surveillance, clotting / coagulation / accumulation of Crinone gel has been reported. These phenomena are usually not serious and manifest themselves in the form of beige to brownish, lumpy and sometimes cloudy white secretions. The clotting / coagulation / accumulation of the gel can be accompanied by irritation of the vagina, pain and swelling; very rarely it can also cause cramps and vaginal bleeding.

Contra-indications
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Undiagnosed vaginal bleeding
- Known or suspected malignancy of the breast or genitalia
- Porphyria.
- Thrombophlebitis, thromboembolic disorders, cerebral apoplexy or an anamnesis with these disorders.
- Missed abortion.

Special warnings and precautions for use
Gynecological checks must be carried out prior to and regularly during treatment with this pharmaceutical product; as part of these controls, in particular, it should be ruled out that hyperplasia of the endometrium occurs during a longer-term treatment. During the physical examination that precedes treatment, special attention must be paid to the breasts and pelvic organs, and a smear must be made according to Papanicolaou.

If an imminent abortion occurs during treatment with Crinone, the viability of the embryo must be determined by measuring rising HCG titers and / or ultrasound examination.

In the event of severe hepatic impairment, the pharmaceutical product should be used with caution.

In the case of breakthrough bleeding, as in all cases of irregular bleeding, it must be checked whether there is a non-functional cause. In all cases of undiagnosed vaginal bleeding, adequate diagnostic measures must be performed.

Since progestagens can cause a certain degree of fluid retention, careful observation of conditions that may be affected (e.g. epilepsy, migraine, asthma, cardiac and renal impairment) is necessary.

Patients who have experienced a psychological depression in the past should be closely monitored and the pharmaceutical product should be discontinued if the depression is severe.

A decrease in glucose tolerance has been observed in a small number of patients treated with pharmaceutical products containing a combination of estrogen and progestin. The mechanism of this decrease is unknown. For this reason, patients with diabetes must be closely monitored when treated with progestin.

The doctor must be aware of early manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism and retinal thrombosis). If one of these thrombotic conditions develops or is suspected, the administration of the pharmaceutical product should be stopped immediately. Patients with risk factors for the development of thrombotic disorders should be closely monitored.

Fertility, pregnancy and lactation
Pregnancy
The use of Crinone during pregnancy is not indicated, except as part of an ART scheme during early pregnancy.

Breastfeeding
The use of Crinone while breastfeeding is not recommended.

Fertility
Crinone is indicated in adults as a supplement to progesterone during the luteal phase as part of an ART (assisted reproductive technology) procedure (see section 4.1).

Effects on ability to drive and use machines
Fatigue may occur while taking Crinone.
Caution is advised if a car is driven or a machine is operated during pregnancy.
In particular, it should not be forgotten that the use of alcohol can further affect the ability to drive a car.

Interaction with other pharmaceutical products and other forms of interaction
This pharmaceutical product should not be used at the same time as other intravaginal treatments.
No interactions studies have been conducted.

Overdose
Overdose is not to be expected because each dose is administered through an individual disposable applicator. However, if overdose has occurred, treatment with Crinone must be stopped.