Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Vagifem 25 micrograms vaginal tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vaginal tablet contains:

Estradiol hemihydrate equivalent to estradiol 25 micrograms.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Vaginal tablet.

White, film coated, biconvex tablet, engraved with 'NOVO 279' on one side. Diameter 6mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of vaginal atrophy due to oestrogen deficiency in postmenopausal women (see section 5.1).

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

4.2 Posology and method of administration

Vagifem is administered intravaginally as a local oestrogen therapy by use of an applicator.

Initial dose: One vaginal tablet daily for 2 weeks.
Maintenance dose: One vaginal tablet twice a week.

Treatment may be started on any convenient day.

If a dose is forgotten, it should be taken as soon as the patient remembers. A double dose should be avoided.

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

Vagifem is a local vaginal therapy and in women with an intact uterus, progestagen treatment is not necessary (however see Section 4.4, Special warnings and precautions for use, endometrial hyperplasia and carcinoma).

Vagifem may be used in women with or without an intact uterus.

Vaginal infections should be treated before start of the Vagifem therapy.

Administration:

1. Open the blister pack at the plunger end.
2. Insert the applicator in the vagina until resistance is met (8-10cm).
3. Release the tablet by pressing the plunger.

4. Withdraw the applicator and discard.

4.3 Contraindications

- Known, past or suspected breast cancer
- Known, past or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer)
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency, see section 4.4)
- Active or recent arterial thromboembolic disease (e.g. angina, mycardial infarction)
- Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal.
- Known hypersensitivity to the active substance or to any of the excipients
- Porphyria.

4.4 Special warnings and precautions for use

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

Medical examination/follow-up

Before initiating or reinstituting hormone therapy, a complete personal and family medical history should be obtained. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman.

Women should be advised what changes in their breasts should be reported to their doctor or nurse. Investigations including appropriate imaging tools, e.g. mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

The pharmacokinetic profile of Vagifem shows that there is very low systemic absorption of estradiol during treatment (see Section 5.2), however, being a HRT product the following need to be considered, especially for long term or repeated use of this product.

Conditions which need supervision

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

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

The pharmacokinetic profile of Vagifem shows that there is very low absorption of estradiol during treatment (see Section 5.2). Due to this, the recurrence or aggravation of the above-mentioned conditions is less likely than with systemic oestrogen treatment.

Reasons for immediate withdrawal of therapy

Therapy should be discontinued in case a contra-indication is discovered and in the following situations:

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

Vagifem is a locally acting low dose estradiol preparation and therefore the occurrence of the below mentioned conditions is less likely than with systemic oestrogen treatment.

Endometrial hyperplasia and carcinoma

Women with an intact uterus with abnormal bleeding of unknown aetiology or women with an intact uterus who have previously been treated with unopposed oestrogens should be examined with special care in order to exclude hyperstimulation/malignancy of the endometrium before initiation of treatment with Vagifem.

In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among systemic oestrogen-only users varies from 2- to 12- fold compared with non-users, depending on both duration of treatment and on oestrogen dose. After stopping treatment, risk may remain elevated for at least 10 years.

During Vagifem treatment, a minor degree of systemic absorption may occur in some patients, especially during the first two weeks of once daily administration. However, average plasma E2 concentrations ($C_{ave\ (0\text{-}24)}$) at all evaluated days remained within the normal postmenopausal range in all subjects (see section 5.2).

Endometrial safety of long-term (more than one year) or repeated use of local vaginally administered oestrogen is uncertain. Therefore, if repeated, treatment should be reviewed at least annually, with special consideration given to any symptoms of endometrial hyperplasia or carcinoma.

As a general rule, oestrogen replacement therapy should not be prescribed for longer than one year without another physical, including gynaecological examination being performed. If bleeding or spotting appears at any time on therapy, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

The woman should be advised to contact her doctor in case bleeding or spotting occurs during treatment with Vagifem.

Unopposed oestrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore caution is advised when using this product in women who have undergone hysterectomy because of endometriosis, especially if they are known to have residual endometriosis.

Breast Cancer

The overall evidence suggests an increased risk of breast cancer in women taking combined oestrogen-progestagen and possibly also oestrogen-only HRT, that is dependent on the duration of taking HRT.
The WHI trial found no increase in risk of breast cancer in hysterectomised women using oestrogen-only HRT.
Observational studies have mostly reported a small increase in risk of having breast cancer diagnosed that is substantially lower than found in users of oestrogen-progestagen combinations.
The excess risk becomes apparent within a few years of use but returns to baseline within a few (at most five) years after stopping treatment.
A relationship between breast cancer risk and low dose local vaginal oestrogen therapy is uncertain.
HRT, especially oestrogen-progestagen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Ovarian cancer

Ovarian cancer is much rarer than breast cancer. Long-term (at least 5-10 years) use of oestrogen-only HRT products has been associated with a slightly increased risk of ovarian cancer. Some studies including the WHI trial suggest that the long-term use of combined HRTs may confer a similar or slightly smaller risk (see Section 4.8).
A relationship between ovarian cancer risk and low dose local vaginal oestrogen therapy is uncertain.

Venous thromboembolism

HRT is associated with a 1.3-3 fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later.

Patients with known thrombophilic states have an increased risk of VTE and HRT may add to this risk. HRT is therefore contraindicated in these patients (see section 4.3).

Generally recognised risk factors for VTE include use of oestrogens, older age, major surgery, prolonged immobilisation, obesity (BMI>30 kg/$m^{2)}$, pregnancy/postpartum period, systemic lupus erythematosus (SLE) and cancer. There is no consensus about the possible role of varicose veins in VTE.

A relationship between venous thromboembolism and low dose local vaginal oestrogen therapy is uncertain.

As in all postoperative patients, prophylactic measures need to be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery, temporarily stopping HRT 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised.

In women with no personal history of VTE but with first degree relative with a history of thrombosis at young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening).

If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is 'severe' (e.g. antithrombin, protein S, or protein C deficiencies or a combination of defects) HRT is contraindicated.

Women already on chronic anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.

If VTE develops after initiating therapy the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

Coronary artery disease (CAD)

There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined oestrogen-progestagen or oestrogen-only.
Randomised controlled data found no increased risk of CAD in hysterectomised women using oestrogen-only therapy.

Ischaemic stroke

Combined oestrogen-progestagen and oestrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT increase with age.

A relationship between ischaemic stroke and low dose local vaginal oestrogen therapy is uncertain.

Other conditions

Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.

Women with pre-existing hypertriglyceridaemia should be followed closely during oestrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this condition.

The relationship between pre-existing hypertriglyceridaemia and low dose local vaginal oestrogen therapy is unknown.

Oestrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone (as measured by protein-bound iodine (PBI)), T4 levels (by column or by radio-immunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex-hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

The minimal systemic absorption of estradiol with local vaginal administration (see Section 5.2 Pharmacokinetic Properties) is likely to result in less pronounced effects on plasma binding proteins than with systemic hormones.

HRT does not improve cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using continuous combined or oestrogen-only HRT after the age of 65.

Intravaginal applicator may cause minor local trauma, especially in women with serious vaginal atrophy.

4.5 Interaction with other medicinal products and other forms of interaction

As the oestrogen in Vagifem is administered within the vagina and due to the low levels of estradiol released, it is unlikely that any clinically relevant drug interactions will occur with Vagifem.

However, the metabolism of oestrogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Herbal preparations containing St. John's Wort (Hypericum perforatum) may induce the metabolism of oestrogens.

4.6 Fertility, pregnancy and lactation

Vagifem is not indicated during pregnancy. If pregnancy occurs during medication with Vagifem, treatment should be withdrawn immediately. The results of most epidemiological studies to date relevant to inadvertent foetal exposure to oestrogens indicate no teratogenic or foetotoxic effect.

Lactation
Vagifem is not indicated during lactation.

4.7 Effects on ability to drive and use machines

No effects known.

4.8 Undesirable effects

More than 640 patients have been treated with Vagifem in clinical trials, including over 200 patients treated from 28 and 64 weeks. Well known oestrogen-related adverse effects which occurred with a higher frequency in the treated

group as compared with the placebo group, are presented as “Common (>1/100, <1/10).

The spontaneous reporting rate on Vagifem corresponds to approximately 1 case per 10,000 patient years. Adverse events for which an increased frequency has not been observed in clinical trials, but which have been spontaneously reported, and which on an overall judgement are considered possibly related to Vagifem treatment are therefore presented as “Very rare (<1/10,000).

Post marketing experience is subject to under-reporting especially with regard to trivial and well-known adverse drug reactions. The presented frequencies should be interpreted in that light.

The most commonly reported adverse drug reactions are: vaginal discharge and vaginal discomfort. Oestrogen-related adverse events such as breast pain, peripheral oedema and postmenopausal bleedings are most likely to present at the beginning of Vagifem treatment.

System organ class	**Common ≥1/100; <1/10**	**Uncommon ≥1/1000; <1/100**	**Rare ≥1/10,000; <1/1000**
Infections and infestations	Genital candidiasis or vaginitis, see also “Reproductive system and breast disorders”		
Neoplasms benign and malignant (incl. cysts and polyps)			
Immune system disorders			
Metabolism and nutrition disorders			
Psychiatric disorders			
Nervous system disorders	Headache		
Vascular disorders			
Gastrointestinal disorders	Nausea, abdominal pain, abdominal distension or abdominal discomfort Dyspepsia Vomiting Flatulence		
Skin and subcutaneous tissue disorders			
Reproductive system and breast disorders	Vaginal haemorrhage, vaginal discharge or vaginal		

	discomfort Breast oedema, breast enlargement, breast pain or breast tenderness		
General disorders and administration site conditions	Oedema peripheral		
Investigations			

Post-marketing experience:

In addition to the above mentioned adverse drug reactions, those presented below have been spontaneously reported for patients being treated with Vagifem 25 micrograms, and are considered possibly related to treatment. The reporting rate of these spontaneous adverse reactions is very rare (<1/10,000 patient years).

- Neoplasms benign and malignant (incl. cysts and polyps): breast cancer, endometrial cancer
- Immune system disorders: generalized hypersensitivity reactions (e.g. anaphylactic reaction/shock)
- Metabolism and nutrition disorders: fluid retention
- Psychiatric disorders: insomnia, depression
- Nervous system disorders: migraine aggravated
- Vascular disorders: deep venous thrombosis
- Gastrointestinal disorders: diarrhoea
- Skin and subcutaneous tissue disorders: urticaria, rash erythematous, rash pruritic, rash NOS, genital pruritus
- Reproductive system and breast disorders: endometrial hyperplasia, vaginal irritation, vaginal pain, vaginismus, vaginal ulceration
- General disorders and administration site conditions: drug ineffective
- Investigations: weight increased, blood oestrogen increased.

Other adverse reactions have been reported in association with oestrogen treatment. Risk estimates have been drawn from systemic exposure and it is not known how these apply to local treatments:

- Myocardial infarction, congestive heart disease
- Stroke
- Gall bladder disease
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura
- Increase in size of fibroids
- Epilepsy
- Libido disorder
- Deterioration of asthma
- Probable dementia over the age of 65 (see section 4.4).

Breast cancer risk

-

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

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestagen therapy for more than 5 years.
- Any increased risk in users of oestrogen-only therapy is substantially lower than that seen in users of oestrogen-progestagen combinations.
- The level of risk is dependent on the duration of use (see section 4.4).
- Results of the largest randomised placebo-controlled trial (WHI-study) and largest epidemiological study (MWS) are presented.

-

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

Age range (years)	Incidence per 1000 never-users of HRT over a 5 year period*	Risk ratio and 95% CI #	Additional cases per 1000 HRT users over 5 years (95% CI)
		Oestrogen only HRT	
50 – 65	9 – 12	1.2	1 - 2 (0 - 3)
		Combined oestrogen-progestagen	
50 - 65	9 - 12	1.7	6 (5-7)
* Taken from baseline incidence rates in developed countries. # Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use. Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.			

-

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

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95% CI	Additional cases per 1000 HRT users over 5 years (95% CI)
		CEE oestrogen-only	
50 – 79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0) *
		CEE+MPA oestrogen & progestagen	
50 - 79	14	1.2 (1.0-1.5)	+4 (0-9)

* WHI study in women with no uterus, which did not show an increase in risk of breast cancer
‡When the analysis was restricted to women who had not used HRT prior to the study there was no increased risk apparent during the first 5 years of treatment: after 5 years the risk was higher than in non-users.

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

Long-term use of oestrogen-only and combined oestrogen-progestogen HRT has been associated with a slightly increased risk of ovarian cancer. In the Million Women Study, 5 years of HRT resulted in 1 extra case per 2500 users.

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

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

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95% CI	Additional cases per 1000 HRT users
Oral oestrogen-only*			
50-59	7	1.2 (0.6 - 2.4)	1 (-3 – 10)
Oral combined oestrogen-progestagen*			
50-59	4	2.3 (1.2-4.3)	5 (1-13)

* Study in women with no uterus

Risk of coronary artery disease

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

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

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

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

* No differentiation was made between ischaemic and haemorrhagic stroke

4.9 Overdose

No cases of overdose have been reported.

Vagifem 25 µg is intended for intravaginal use and the dose of estradiol is very low. Overdose is therefore unlikely, but if it occurs, treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ATC code G03C A03
Natural and semisynthetic oestrogens, plain (for vaginal use).

The active ingredient, synthetic 17β−estradiol, is chemically and biologically identical to endogenous human estradiol.

Endogenous 17β−estradiol induces and maintains the primary and secondary female sexual characteristics. The biological effect of 17β−estradiol is carried out through a number of specific oestrogen receptors. The steroid receptor complex is bound to the cell's DNA and induces synthesis of specific proteins.

Maturation of the vaginal epithelium is dependent upon oestrogens. Oestrogens increase the number of superficial and intermediate cells and decrease the number of basal cells in vaginal smear.

Oestrogens maintain vaginal pH around normal range (4.5) which enhances normal bacterial flora.

5.2 Pharmacokinetic properties

Absorption

Oestrogens are well absorbed through the skin, mucous membranes, and the gastrointestinal tract. After vaginal administration, estradiol is absorbed circumventing first-pass metabolism.

A 12 weeks single-centre randomised, open label, multiple dose, parallel-group trial was conducted to evaluate the extent of systemic absorption of estradiol from the Vagifem 25 µg E2 tablet . Subjects were randomized 1:1 to receive

either 25 µg E2 (Vagifem) or 10 µg E2. Plasma levels of estradiol (E2), oestrone (E1) and oestrone sulfate (E1S) were determined at Day -1 (pre-dose), Day 1 (after 1st dosing), Day 14 (after 14 days of once-daily dosing), Day 82 (pre-dose after 10 weeks twice-weekly treatment) and Day 83 (post-dose after 10 weeks twice-weekly treatment).

The primary bioavailability endpoint of the clinical trial was $AUC_{(0-24)}$ for plasma E2 levels (see Table 1): this parameter indicated higher systemic oestradiol levels for Vagifem 25 µg as compared to baseline on treatment days 1, 14 and 83. However, average plasma E2 levels ($C_{ave(0-24)}$) at all time points overall remained below 20 pg/ml. The data from day 82 indicate that in the long term, systemic oestradiol levels do not accumulate during twice weekly maintenance therapy (see Table 1).

Table 1 Values of PK parameters from plasma Estradiol (E2) concentrations: Study VAG-1850

	$AUC_{(0-24)}$ pg.h/mL(geom. mean)	**$C_{ave(0-24)}$ pg/mL (geom.mean)**
Day -1	96.66	4.03
Day 1	476.14	19.84
Day 14	438.87	18.29
Day 82	48.13	2.01
Day 83	225.94	9.41

The levels of oestrone seen during 12 weeks of Vagifem 25 µg administration do not show any accumulation of oestrone.

Distribution
The distribution of exogenous oestrogens is similar to that of endogenous oestrogens. Oestrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Oestrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.

Biotransformation
Exogenous oestrogens are metabolized in the same manner as endogenous oestrogens. The metabolic transformations take place mainly in the liver. Estradiol is converted reversibly to oestrone, and both can be converted to estriol, which is the major urinary metabolite. In postmenopausal women, a significant portion of the circulating oestrogens exist as sulphate conjugates, especially oestrone sulfate, which serves as a circulating reservoir for the formation of more active oestrogens.

Elimination
Estrogen metabolites are primarily excreted in the urine as glucuronides and sulfates.

5.3 Preclinical safety data

17β−estradiol is a well−known substance in humans. Non-clinical studies provided no additional data of relevance to clinical safety beyond those already included in other sections of the SmPC. performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:
Hypromellose
Lactose monohydrate
Maize starch
Magnesium stearate

Film-coating:
Hypromellose
Macrogol 6000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Three years.

6.4 Special precautions for storage

Store below 25^{o}C. Do not refrigerate.

6.5 Nature and contents of container

Each tablet is contained in a disposable single-use polyethylene/polypropylene applicator. The applicators are packed separately in PVC/aluminium foil blisters.

15 vaginal tablets with applicators.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsvaerd
Denmark

8 MARKETING AUTHORISATION NUMBER

PA 218/30/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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