Applicant	**:**	Sandoz SA (Pty) Ltd	V1.2 (18 July 2022)
Proprietary name	**:**	Estradot 25, 37.5, 50, 75 and 100	
Dosage form and strength	**:**	Transdermal Patch Each transdermal patch contains 0,39, 0,585 ,0,78 ,1,17, 1,56 mg of estradiol hemihydrate	
Date of submission	**:**	18 July 2022	

PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

PROPRIETARY NAMES AND DOSAGE FORM:

ESTRADOT® 25 (Transdermal Patch)

ESTRADOT® 37,5 (Transdermal Patch)

ESTRADOT® 50 (Transdermal Patch)

ESTRADOT® 75 (Transdermal Patch)

ESTRADOT® 100 (Transdermal Patch)

COMPOSITION:

ESTRADOT contains estradiol in a transdermal patch, i.e. an adhesive patch designed for application to an area of intact skin.

Five ESTRADOT Transdermal delivery system patches are available:

	Nominal delivery µg/day	***Estradiol (as hemihydrate) mg***	***Surface area (cm^2)***
ESTRADOT 25	25	0,39	2,5
ESTRADOT 37,5	37,5	0,585	3,75
ESTRADOT 50	50	0,78	5
ESTRADOT 75	75	1,17	7,5
ESTRADOT 100	100	1,56	10

The composition of each transdermal patch per unit area is identical. ESTRADOT patches are replaced twice weekly i.e. every 3 to 4 days.

Inactive ingredients: adhesive layer: (BIO-PSA silicone adhesive, dipropylene glycol, Gelva 788 acrylic adhesive, oleyl alcohol, povidone), backing layer film: (ethylene vinyl acetate and vinylidine chloride / methyl acrylate copolymer layers) and release liner: (fluoropolymer-coated polyester (removed before use)).

Sugar free.

PHARMACOLOGICAL CLASSIFICATION:

A 21.8.1 Estrogens

PHARMACOLOGICAL ACTION:

Pharmacokinetic properties:

Following oral administration, estradiol undergoes extensive first pass metabolism in the gut wall and the liver to less active metabolites such as estriol and estrone; the bioavailability is only 3 to 5 %.

Estradiol is more than 50 % bound to plasma proteins such as sex-hormone-binding globulin and albumin. It is excreted in the urine as sulfate and glucuronide esters along with a small proportion of estradiol and several other metabolites. Only a small amount is excreted in faeces.

In studies in postmenopausal women with application of 2,5, 3,75, 5 and 10 cm^2 ESTRADOT patches, average peak estradiol serum levels (C_{max}) were approximately 25 pg/ml, 35 pg/ml, 50 to 55 pg/ml and 95 to 105 pg/ml, respectively. Linear pharmacokinetics has been demonstrated for estradiol following transdermal administration.

Since estradiol has a short half-life (approximately one hour), serum concentrations of estradiol and estrone returned to baseline values within 24 hours following removal of the patch.

At steady state, after repeated applications of 5 cm^2 (50 micrograms/day) ESTRADOT patches, estradiol C_{max} and C_{min} values (57 and 28 pg/ml, respectively) were similar to those in the single application study, while estrone C_{max} and C_{min} values were lower (42 and 31 pg/ml, respectively).

Preclinical safety data:

The toxicity profile of estradiol has been well established. Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

Pharmacodynamic properties:

The active substance in ESTRADOT, 17β-estradiol, is chemically and biologically identical to the endogenous human 17β-estradiol.

INDICATIONS:

- Estrogen replacement therapy for the treatment of the symptoms of natural or surgically induced menopause.
- To reduce the risk of postmenopausal osteoporosis (see sections “DOSAGE AND DIRECTIONS FOR USE”, “WARNINGS” and “Special precautions”).

In women with an intact uterus, estrogens sghould always be supplemented by administration of a progestogen.

CONTRAINDICATIONS:

ESTRADOT should not be used by women with any of the following conditions:

- Known hypersensitivity to estrogens or to any of the excipients.
- Known or suspected pregnancy.
- Breastfeeding.
- Undiagnosed abnormal vaginal bleeding.
- Known or suspected breast cancer.
- History of breast cancer.
- Known or suspected cancer of the endometrium or other estrogen-dependent neoplasia.
- Existing or previous severe hepatic disease.
- History of or current venous thromboembolism (e.g. deep vein thrombosis, pulmonary embolism).
- Known thrombophilic disorders or thrombophlebitis.
- History of or current arterial thromboembolic disease (e.g. coronary heart disease, stroke).
- Porphyria.
- Depression not well controlled with treatment.
- A history of depression with the use of hormonal containing medicines irrespective of indication, dosage formulation and route of administration.

WARNINGS:

Osteoporosis:

When initiating HRT for the prevention of osteoporosis, careful consideration should be given to the benefits versus the risks for the individual. Potential alternative therapies should be considered if the risks outweigh the benefits. Periodic re-evaluation for continuing treatment is recommended.

Contact sensitisation:

Contact sensitisation is known to occur with all topical applications. Although it is extremely rare, women who develop contact sensitisation to any of the components of the patch should be warned that a severe hypersensitivity reaction may occur with continuing exposure to the causative agent.

Cardiovascular disease:

HRT should not be used to prevent cardiovascular disease.

Large clinical trials (Women's Health Initiative and Heart and Estrogen/Progestin Replacement study) evaluated the risk of cardiovascular events with the HRT products used in these studies.

The Women's Health Initiative (WHI) studies were randomised clinical trials conducted with either continuous combined oral conjugated equine estrogens (CEO) and medroxyprogesterone acetate (MPA) for an average follow-up of 5,2 years, or with oral conjugated equine estrogen (CEE) for an average follow-up of 6,8 years. In the WHI continuous combined oral HRT trial, the absolute excess risk of coronary heart disease was 7 additional cases per 10 000 person-years (37 versus 30) in HRT-treated women and the relative risk was 1,29.

In the WHI estrogen-only HRT trial, the use of CEE alone did not affect coronary heart disease incidence in postmenopausal women.

In addition, both WHI studies showed an increased incidence of stroke. In the trial of continuous combined oral conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA), the absolute excess risk was 8 additional cases per 10 000 person-years (29 versus 21) in HRT-treated women and the relative risk was 1,41. The absolute excess risk in

the trial of continuous oral conjugated equine estrogens (CEE) was 12 additional cases per 10 000 person-years (44 versus 32) in HRT-treated women and the relative risk was 1,39.

The Heart and Estrogen/Progestin Replacement Study (HERS), which is a controlled clinical trial of secondary prevention in postmenopausal women with documented heart disease conducted with CEO and MPA, showed an increased risk of cardiovascular events in the first year of use and no cardiovascular benefit thereafter.

For transdermal estrogen-only and estrogen-progestogen combined HRT products, there are no randomised controlled trials to date assessing the HRT-associated risk of cardiovascular morbidity or mortality, or stroke. Therefore, there are no data to support the conclusion that the frequency of cardiovascular events and stroke is different with ESTRADOT.

Breast cancer:

Randomised controlled trials and epidemiological studies have reported an increased risk of breast cancer in women taking HRT.

Women using estrogen-progestogen combined HRT had a possibly higher risk as compared with women who used unopposed estrogens. The excess risk of breast cancer increases with the duration of intake of estrogen-only and estrogen-progestogen combined HRT.

There is evidence arising from the WHI continuous combined study (see subsection Cardiovascular disease) which shows an absolute excess risk of invasive breast cancer of 8 additional cases per 10 000 person-years (38 versus 30) in the HRT-treated women and a relative risk of 1,26.

A meta-analysis reanalysed 51 epidemiological studies conducted between the 1970s and the early 1990s. The cumulative incidence of breast cancer between the ages of 50 and 70 in non-users of HRT is about 45 per 1 000 women. The cumulative excess numbers of breast cancers diagnosed between these ages per 1 000 women who began use of HRT at age 50 to 70 and used it for 5, 10, and 15 years, are estimated to be 2, 6, and 12, respectively.

The number of additional cases of breast cancer is broadly similar for women who start HRT regardless of age at start of treatment (between ages of 45 and 65). The excess risk seems to return to baseline in the course of about five years after stopping treatment.

For transdermal estrogen-only and estrogen-progestogen combined HRT products, no large randomised clinical trials to date have assessed the HRT-associated risk of breast cancer. Therefore, there are no data to support the conclusion that the frequency of breast cancer is different with ESTRADOT.

Ovarian cancer:

In some epidemiological studies, the long-term use of opposed and unopposed estrogens in hysterectomised and non-hysterectomised women has been associated with an increased risk of being diagnosed with ovarian cancer. It is uncertain whether long-term use of combined HRT (estrogens and progestogens) confers a different risk than estrogen-only HRT products.

Endometrial cancer:

The risk of endometrial cancer in users of unopposed estrogens who have an intact uterus is greater than in non-users and appears to depend on the duration of treatment and the estrogen dose. The greatest risk appears to be associated with prolonged use. It has been shown that adequate concomitant progestogen therapy lowers the incidence of endometrial

hyperplasia and therefore the potential risk of endometrial carcinoma associated with prolonged use of estrogen therapy.

Dementia:

In a randomised placebo-controlled ancillary study of the WHI, the Women's Health Initiative Memory Study (WHIMS), women aged 65 and older (average age 71) treated with oral CEO and MPA for an average follow-up of 4 years were reported to have a two-fold increase in the risk of developing probable dementia. The absolute excess risk of probable dementia was 23 additional cases per 10 000 person-years (45 versus 22) in CEO/MPA treated women and the relative risk was 2,05.

In a randomised, placebo-controlled, estrogen alone ancillary study of the WHI (WHIMS), the absolute excess risk of probable dementia after an average follow-up of 5,2 years was 12 additional cases per 10 000 person-years (37 versus 25) in CEE treated women and the relative risk was 1,49, which did not reach statistical significance (p = 0,18) compared to placebo.

Since both sub-studies were conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women.

For transdermal estrogen-only or estrogen-progestogen combined products, no large randomised clinical trials have assessed the HRT-associated risk of probable dementia to date. Therefore, there are no data to support the conclusion that the frequency of probable dementia is different with ESTRADOT.

Venous thromboembolism:

Estrogen-only and estrogen-progestogen combined HRT are associated with a higher risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism.

Three randomised controlled trials (WHI estrogen-alone, WHI combined HRT and HERS) and epidemiological studies have found a two- to threefold higher risk for users compared with non-users.

The WHI continuous combined study (see subsection “Cardiovascular disease”) showed an increased incidence of pulmonary embolism. The absolute excess risk was 8 additional cases per 10 000 person-years (15 versus 7) in HRT-treated women and the relative risk was 2,13.

The increase in risk was found only in current users and did not persist in former users. The risk appeared to be higher in the first years of use compared to later years.

For non-users, it is estimated that the number of cases of VTE that would occur over a 5-year period is about 3 per 1 000 women aged 50 to 59 years and 8 per 1 000 women aged 60 to 69 years. It is estimated that in healthy women who use HRT for 5 years, the number of additional cases of VTE would be between 2 and 6 per 1 000 women aged 50 to 59 years and between 5 and 15 per 1 000 women aged 60 to 69 years.

Risk/benefit should therefore be carefully weighed in consultation with the individual when prescribing HRT to women with a risk factor for the occurrence of VTE that is not already mentioned under “CONTRAINDICATIONS”.

Generally recognised risk factors for VTE include a personal history or positive family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic

predisposition) of thromboembolic disease, severe obesity (Body Mass Index > 30 kg/m^2) and systemic lupus erythematosus (SLE). The risk of VTE also increases with age. There is no consensus about the possible role of varicose veins in VTE.

A history of recurrent spontaneous abortion should be investigated to exclude thrombophilic predisposition. In women in whom this diagnosis is confirmed, the use of HRT is viewed as contraindicated.

The risk of VTE may be temporarily increased with prolonged immobilisation, major elective or posttraumatic surgery, or major trauma. In women on HRT, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Depending on the nature of the event and the duration of the immobilisation, consideration should be given to temporarily stopping HRT several weeks (four to six weeks) earlier, if possible. The treatment should not be restarted until the woman is completely mobile.

Women should be told to contact their doctor immediately if they become aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

If venous thromboembolism (VTE) develops after initiating therapy, the medicine should be discontinued.

Depression:

Women with a history of depression who use hormonal containing products should be carefully observed and the medicinal product discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while taking hormonal containing products should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug-related.

Depressed mood and depression are well-known undesirable effects of hormonal containing products (see “CONTRAINDICATIONS”). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

INTERACTIONS:

The metabolism of estrogens and progestogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P-450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine), meprobamate, phenylbutazone and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).

Caution should be used if the woman is receiving protease inhibitors (e.g. ritonavir and nelfinavir), which are known as strong inhibitors of cytochrome P-450 enzymes, and 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 estrogens and progestogens.

Clinically, increased metabolism of estrogens and progestogens may lead to decreased effects and changes in the uterine bleeding profile.

With transdermal HRT administration, the first-pass effect in the liver is avoided and, thus transdermally applied estrogens may be less affected by enzyme inducers than oral hormones.

Some laboratory tests may be influenced by estrogen therapy, such as tests for glucose tolerance or thyroid function.

PREGNANCY AND LACTATION:

Pregnancy:

ESTRADOT must not be used during pregnancy.

Lactation:

ESTRADOT must not be used while breast-feeding. Both estrogens and progestogens cause foetal harm when administered to a pregnant woman.

DOSAGE AND DIRECTIONS FOR USE:

Adults and elderly:

Dosage: Hormone Replacement Therapy (HRT) involving either estrogen- only or estrogen-progestogen combined therapy should only be continued as long as the benefits outweigh the risks for the individual.

ESTRADOT should be applied every 3 to 4 days (i.e. twice weekly).

Climacteric symptoms:

ESTRADOT is available in five strengths: 25, 37,5, 50, 75 and 100 microgram/day. Treatment is usually initiated with an ESTRADOT 50 patch. Depending on the clinical response the dose should then be adjusted to the woman’s individual needs. If, after three months, there is an insufficient response in the form of alleviated symptoms, the dose should be increased. If symptoms of overdose arise (e.g. tender breasts) the dose must be decreased. Maintenance therapy must always be at the lowest effective dose.

Prevention of postmenopausal osteoporosis: Treatment should be initiated with an ESTRADOT 50 patch. Dose adjustments can be made by using other strengths of ESTRADOT. The lowest effective dose should be used for maintenance therapy.

General instructions:

ESTRADOT is administered as continuous therapy (uninterrupted application twice weekly).

In women with an intact uterus, ESTRADOT should be combined with a progestogen approved for addition to estrogen treatment as follows:
The progestogen is added either for the last 12 to 14 days of every 4-week cycle (continuous-sequential) or every day without interruption (continuous-combined).

In women not currently taking oral estrogens or in women switching from another estradiol transdermal therapy, treatment with ESTRADOT may be initiated at any convenient time. In women who are currently taking oral estrogens, treatment with ESTRADOT should be initiated one week after withdrawal of oral hormone replacement therapy, or sooner if menopausal symptoms reappear within one week.

Method of administration:

The adhesive side of ESTRADOT should be placed on a clean, dry area of the abdomen.
ESTRADOT should not be applied to the breasts.
ESTRADOT should be replaced twice weekly. The site of application must be rotated, with an interval of at least 1 week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. The waistline should be avoided, since tight clothing may dislodge the patch. The patch should be applied immediately after opening the sachet and removing the protective liner. The patch should be pressed firmly in place with the palm

of the hand for about 10 seconds, making sure there is good contact, especially around the edges.

In the event that a patch should fall off, the same patch may be reapplied. If necessary, a new patch may be applied. In either case, the original treatment schedule should be continued.

If a woman has forgotten to apply a patch, she should apply a new patch as soon as possible. The subsequent patch should be applied according to the original treatment schedule. The interruption of treatment might increase the likelihood of recurrence of symptoms.

Children: ESTRADOT should not be used in children.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side effects:

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000) very rare (<1/10,000), including isolated reports.

Table 1:

Neoplasms benign, malignant and unspecified (including cysts and polyps) Uncommon:	Breast cancer.
Immune system disorders Not known [(1)]:	Hypersensitivity.
Psychiatric disorders Common:	Mood changes, including depression
Nervous system disorders	

Common:	Headache, migraine, dizziness.
Gastro-intestinal disorders Common: Uncommon:	 Nausea, abdominal pain, abdominal cramps. Vomiting.
Skin and subcutaneous tissue disorders Uncommon: Not known [(1)]:	 Alopecia, hirsutism. Erythema multiforme, erythema nodosum.
Reproductive system and breast disorders Very common: Common: Uncommon:	 Breast tenderness. Menstrual disorders, (changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow), metrorrhagia, cervical discharge breast enlargement. Genital candidiasis, uterine leiomyoma.
General disorders and administration site conditions Very common: Common: Uncommon:	 Application site reaction (at the patch application site, observed after removing the patch by peeling from the skin). Weight change, oedema, pruritus and rash. (around the application site). Libido increased or decreased.
Reported in post-marketing experience. Not known[(1)]:	Suicidal thoughts/behaviour and suicide.

[(1)] Frequency, not known

Other adverse reactions have been reported in association with some estrogen-progestogen treatments:

- Estrogen-dependent neoplasms, benign and malignant, e.g. endometrial cancer.
- Venous thromboembolism, e.g. deep leg or pelvic venous thrombosis and pulmonary embolism.
- Stroke.
- Myocardial infarction.
- Cholestatic jaundice.
- Gallbladder disease.
- Aggravation of porphyria.
- Dementia.
- Chorea.
- Contact lens intolerance.
- Purpura.
- Chloasma.
- Carbohydrate tolerance decreased.

Special precautions:

Before initiating or re-instituting Hormone Replacement Therapy (HRT), a complete personal and family medical history, and an appropriate physical (including pelvic and breast) examination should be performed (see sections “CONTRAINDICATIONS” and “WARNINGS”).

During treatment, periodic check-ups of a nature and frequency adapted to the individual woman are recommended. A careful appraisal of the risks and benefits should be undertaken over time in women treated with HRT and the need for HRT should be re-evaluated periodically.

Women should be advised that changes in their breasts should be reported to their doctor or nurse. Investigations, including mammography, should be carried out in accordance with currently accepted screening practices and adapted to the clinical needs of the individual woman.

Consideration should be given to the lowest dose and shortest duration of use.

When ESTRADOT therapy is combined with cyclic progestogen administration, there are often occurrences of breakthrough bleeding and spotting during the initial months of treatment.

In all cases of undiagnosed persistent or irregular vaginal bleeding, adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out abnormality and the treatment should be re-evaluated.

Hysterectomised women who require postmenopausal hormone therapy should receive estrogen-only replacement therapy unless otherwise indicated (e.g. endometriosis).

If any of the following conditions are present, or have occurred previously (including during pregnancy or a previous hormone treatment), the woman should be closely monitored in particular: leiomyoma (uterine fibroids) or endometriosis, thromboembolic disorders, heart failure, hypertension, hepatic disorders (e.g. liver adenoma), renal disorders, diabetes mellitus with or without vascular involvement, cholelithiasis, migraine or severe headache, systemic lupus erythematosus, endometrial hyperplasia, epilepsy, asthma, otosclerosis, gall-bladder disease, estrogen-related jaundice and pruritus.

It should be taken into account that these conditions may recur or be aggravated during treatment with estrogens.

Caution is advised when risk factors for estrogen-dependent tumours (e.g. first-degree blood relatives who have ever had breast cancer) are present.

If worsening of any of the above mentioned conditions is diagnosed or suspected during HRT, the benefits and risks of HRT should be reassessed on an individual basis.

Therapy should be discontinued in the following situations: jaundice or deterioration of liver function, a significant increase in blood pressure, new onset of migraine-type headache and pregnancy, or if a condition described under “CONTRAINDICATIONS” develops.

Estrogens may cause fluid retention and therefore, women with cardiac or renal dysfunction should be carefully monitored.

Women with hypertriglyceridaemia should be followed closely during HRT, since rare cases of large increases of plasma triglycerides, leading to pancreatitis, have been reported with oral estrogen therapy in these women.

Although observations to date suggest that estrogens, including transdermal estradiol, do not impair carbohydrate metabolism, diabetic women should be monitored during initiation of therapy until further information is available.

Treatment with estrogens alone increases the incidence of endometrial hyperplasia and the risk of endometrial carcinoma, irrespective of the method of administration. Unopposed estrogen stimulation may lead to premalignant or malignant transformation in the residual foci

of endometriosis. Therefore, the addition of a progestogen to estrogen replacement therapy is recommended in women who have not undergone hysterectomy and who are known to have residual endometriosis.

Women should be advised that ESTRADOT is not a contraceptive, nor will it restore fertility.

Effects on ability to drive and use machines: No known adverse effects on the ability to drive or operate machines have been reported.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Acute overdosage is unlikely due to the mode of administration. The most common symptoms of overdosage in clinical use are breast tenderness and/or vaginal bleeding. If such symptoms occur, a reduction in dosage should be considered. The effects of overdosage can be rapidly reversed by removal of the patch.

IDENTIFICATION:

A rounded rectangle transdermal patch. Pressure-sensitive adhesive with a translucent polymeric backing on one side and a release liner on the other. The patch is contained in a heat-sealed pouch (paper/polyethylene/foil/polyethylene).

PRESENTATION:

Each ESTRADOT transdermal patch is individually sealed in a Coex aluminium foil laminate heat-sealed sachet made of paper/low density polyethylene (LDPE)/aluminium foil/ethylene methacrylic acid copolymer-LDPE.

Sachets may be provided in cartons of 8 or 24.

Not all pack sizes may be marketed.

STORAGE INSTRUCTIONS:

Store at or below 25 °C.

Do not refrigerate or freeze.

The patches should not be stored once opened but should be applied immediately upon removal from the protective sachet.

REGISTRATION NUMBERS:

ESTRADOT 25:	37/21.8.1/0493
ESTRADOT 37,5:	37/21.8.1/0215
ESTRADOT 50:	37/21.8.1/0216
ESTRADOT 75:	37/21.8.1/0217
ESTRADOT 100:	37/21.8.1/0218

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION:

Sandoz SA (Pty) Ltd[1]

Waterfall 5-lr

Magwa Crescent West

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2090

DATE OF PUBLICATION OF THE PACKAGE INSERT:

Date of registration:

ESTRADOT 25:	28 May 2004
ESTRADOT 37,5:	05 September 2003

Applicant	**:**	Sandoz SA (Pty) Ltd	V1.2 (18 July 2022)
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Dosage form and strength	**:**	Transdermal Patch Each transdermal patch contains 0,39, 0,585 ,0,78 ,1,17, 1,56 mg of estradiol hemihydrate	
Date of submission	**:**	18 July 2022	

ESTRADOT 50:	05 September 2003
ESTRADOT 75:	05 September 2003
ESTRADOT 100:	24 October 2003

Date of most recent approval of professional information: 06 September 2021

[1]Company Reg. No.: 1990/001979/07