

**ESTRA-50- estradiol pellet pellet, implantable**  
**ESTRA-25- estradiol pellet pellet, implantable**  
**Advanced Pharmaceutical Technology, Inc.**

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**Estra-50 & Estra-25**

## Warning

### 1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have shown an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for prolonged periods.<sup>1-3</sup> The risk was independent of other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to rapidly expanding use of estrogens during the last decade.<sup>4</sup>

The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment<sup>1</sup> and on estrogen dose.<sup>3</sup> In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy.

Although the evidence must be considered preliminary, one study suggests that cyclic administration in low doses of estrogen may carry less risk than continuous administration,<sup>3</sup> it therefore appears prudent to utilize such a regimen.

Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy.

There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

### 2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY

The use of female sex hormones, both estrogens and progestins, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare.<sup>5,6</sup> This risk has been estimated as not greater than 4 per 1000 exposures.<sup>7</sup> Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis,<sup>8-12</sup> epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes.

Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects.<sup>13-16</sup> One case control study<sup>16</sup> estimated a 4.7 fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormones withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000.

In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is no considerable evidence from well controlled studies that progestins are effective for these uses.

If Estrapel is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

## **DESCRIPTION:**

Estradiol N.F. Pellets contain N.F. 25mg and 50mg for subcutaneous implantation. The pellets are sterile unless vial has been opened or damaged.

Estradiol Pellets are cylindrical, with an approximate diameter of 3.2mm. Pellet therapy has the advantage of high efficiency from the standpoint of the quality of the hormone administered and the further advantage that a single treatment has effect continuously for several months.

## **CLINICAL PHARMACOLOGY:**

Estradiol is one of the more potent of the known estrogenic compounds, identical with the primary estrogenic hormone produced by the human ovary. Estradiol exerts a developmental action on the female generative tract, has an inhibitory effect upon the pituitary in large doses, and produces a marked constitutional effect with an increase in muscular strength, body vigor, and mental acumen. It supplies follicular hormone in cases where estrogenic activity is depressed, insufficient, or absent.

## **INDICATIONS:**

Estradiol is indicated in the treatment of:

### **1. Estrogen deficiency in Hysterectomized Women.**

(There is no evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause, and they should not be used to treat these conditions.)

2. Atrophic vaginitis.
3. Kraurosis vulvae.
4. Female hypogonadism.
5. Female castration.
6. Primary ovarian failure.
7. Breast cancer (for palliation only) in approximately selected women and men with metastatic disease.
8. Postpartum breast engorgement- Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogen.<sup>20,22</sup>

**ESTRADIOL HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).**

## **CONTRAINDICATIONS:**

Estrogens should not be used in women (or men) with any of the following conditions:

1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease.
2. Known or suspected estrogen-dependent neoplasia.
3. Known or suspected pregnancy (See Boxed Warning).

4. Undiagnosed abnormal genital bleeding.
5. Active thrombophlebitis or thromboembolic disorders.
6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast prostatic malignancy).

## WARNINGS:

**1. Induction of malignant neoplasia.** Long term continuous administration of natural and synthetic estrogen in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There is new evidence that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.)

At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast,<sup>18</sup> although a recent long-term followup of a single physician's practice has raised this possibility.<sup>18a</sup> Because of the animal data there is a need for caution, in prescribing estrogens for women with a strong history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms.

**2. Gallbladder disease.** A recent study has reported a 2 to 3 -fold increase in the risk of surgically confirmed gall bladder disease in women receiving postmenopausal estrogens<sup>18</sup> similar to the 2 fold increase previously noted in users of oral contraceptives.<sup>19,24</sup> In the case of oral contraceptives the increased risk appeared after two years of use.<sup>24</sup>

**3. Effects similar to those caused by estrogen-progesterone oral contraceptives.** There are several serious adverse effects of oral contraceptives, most of which have not, up to now, been documented as consequences of postmenopausal estrogen therapy. This may reflect the comparatively low doses of estrogen used in postmenopausal women. It would be expected that the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement are more likely to result in these adverse effects, and, in fact, it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement.

**a. Thromboembolic disease.** It is now well established that users of oral contraceptives have an increased risk of various thromboembolic and thrombotic vascular disease, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction.<sup>24-31</sup> Cases of retinal thrombosis, mesenteric thrombosis and optic neuritis have been reported in oral contraceptive users. There is evidence that the risk of several of these adverse reactions is related to the dose of the drug.<sup>32,33</sup> An increase in risk of postsurgical thromboembolic complications has also been reported in users of oral contraceptives.<sup>34,35</sup> If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

While an increased rate of thromboembolic and thrombotic disease in postmenopausal users of estrogen has not been found,<sup>18,36</sup> this does not rule out that such an increase may be present or that subgroups of women having underlying risk factors or who are receiving relatively large doses of estrogen may have an increased risk. Therefore estrogens should not be used in persons with active thrombophlebitis or thromboembolic disorders and they should not be used (except in treatment of malignancy) in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease and only for those in whom estrogens are clearly needed.

Large doses of estrogens (5mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men<sup>37</sup> to increase the risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis. When estrogen doses of this size are used, any of the thromboembolic and thrombotic adverse effects associated with oral contraceptive use should be considered a clear risk.

**b. Hepatic adenoma.** Benign hepatic adenomas appear to be associated with the use of oral

contraceptives.<sup>38-40</sup> Although benign, and rare, these may rupture and may cause death through intraabdominal hemorrhage. Such lesions have not yet been reported in association with other estrogen or progestin preparations but should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has also been reported in women taking estrogen-containing oral contraceptives.<sup>39</sup> The relationship of this malignancy to these drugs is not known at this time.

**c. Elevated blood pressure.** Increased blood pressure is not uncommon in women using oral contraceptives. There is now a report that this may occur with the use of estrogens in menopause<sup>41</sup> and blood pressure should be monitored with estrogen use, especially if high doses are used.

**d. Glucose tolerance.** A worsening of glucose tolerance has been observed in a significant percentage of patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed while receiving estrogen.

**4. Hypercalcemia.** Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

## **PRECAUTIONS:**

### **A. General Precautions.**

1. A complete medical and family history should be taken prior to initiation of any estrogen therapy. The pretreatment and periodic physical examination should include special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than one year without a physical examination being performed.

2. Fluid retention- Because estrogens may cause some degree of fluid retention, conditions which may be influenced by this factor such as epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.

3. Certain patients may develop undesirable manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc.

4. Oral contraceptives appear to be associated with an increased incidence of mental depression.<sup>24</sup> Although it is not clear whether this is due to the estrogenic or progestogenic component of the contraceptive, patients with a history of depression should be carefully observed.

5. Preexisting uterine leiomyomata may increase in size during estrogen use.

6. The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

7. Patients with a history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving estrogen-containing oral contraceptive therapy. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated.

8. Estrogens may be poorly metabolized in patients with impaired liver function and they should be administered with caution in such patients.

9. Because estrogens influence the metabolism of calcium and phosphorus, they should be used with caution in patients with metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency.

10. Because of the effects of estrogens on epiphyseal closure, they should be used judiciously in young patients in whom bone growth is not complete.

11. Certain endocrine and liver function tests may be affected by estrogen-containing oral contraceptives. The following similar changes may be expected with larger doses of estrogen;

a. Increased sullobromophthalein retention.

- b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
- c. Increased thyroid binding globulin (TGB) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting elevated TBG; free T4 concentration is unaltered.
- d. Impaired glucose tolerance.
- e. Decreased pregnanediol excretion.
- f. Reduced response to metyrapone test.
- g. Reduced serum folate concentration.
- h. Increased serum triglyceride and phospholipid concentration.

### **B. Pregnancy Category X**

(See Contraindications and Boxed Warning).

### **C. Nursing Mothers.**

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

### **ADVERSE REACTIONS:**

(See Warnings regarding induction of neoplasia, adverse effects on the fetus, increased incidence of gall bladder disease, and adverse effects similar to those of oral contraceptives, including thromboembolism.) The following additional adverse reactions have been reported with estrogenic therapy, including oral contraceptives:

1. **Genitourinary System**- breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea; premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis; change in cervical eversion and in degree of cervical secretion; cystitis-like syndrome.
2. **Breasts**- tenderness, enlargement, secretion
3. **Gastrointestinal**- nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice.
4. **Skin**- chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism.
5. **Eyes**- steepening of corneal curvature; intolerance to contact lenses.
6. **CNS**- headache, migraine, dizziness, mental depression, chorea.
7. **Miscellaneous**- increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema, changes in libido.

### **ACUTE OVERDOSAGE:**

Numerous reports of ingestion of large doses of estrogen-containing oral contraceptives by young children indicate that serious ill effects do not occur. Overdosage of estrogen may cause nausea, and withdrawal bleeding may occur in females.

### **DOSAGE AND ADMINISTRATION:**

**Menopausal Syndrome:** In all cases the objective should be determination of the minimum amount of hormone that will maintain the patient symptom-free. With adequate clinical improvement, usually

obtainable in two weeks or less, gradual reduction in dosage are advisable. Subcutaneous implantation-implant one 25mg, Estradiol Pellet and repeat when necessary. The pellets provide constant estrogen levels for approximately 3 months.

**Hypogonadism and Sexual Infantilism:** -1.5mg of estradiol or 1.66mg of estradiol benzoate intramuscularly two to three times weekly. Subcutaneous implantation -implant one 25mg, Pellet and repeat when necessary.

**Amenorrhea and Oligomenorrhea Associated with Hypogonadism:** 1.5mg of estradiol or 1.66mg of estradiol benzoate intramuscularly two to three times weekly during the first two weeks of an arbitrary 28-day menstrual cycle; progesterone is given the last two weeks of the theoretical cycle. This regimen is continued for 3-6 months. The patient then is allowed to go untreated for 2 months to determine whether or not she can maintain the cycle without hormonal therapy. If not, additional courses of therapy as outlined should be prescribed.

**Postpartum Breast Engorgement:** -1.5mg of estradiol or 1.66mg of estradiol benzoate is administered intramuscularly daily beginning at the first sign of engorgement and continuing until the symptoms are controlled. Restriction of fluids and a tight binder should also be employed.

**Inoperable Breast Carcinoma in Postmenopausal Women:** -1.5mg of estradiol or 1.66mg of estradiol benzoate intramuscularly three or more times weekly according to the severity of the pain.

**Carcinoma of the Prostate:** -1.5mg of estradiol or 1.66mg of estradiol benzoate intramuscularly three times weekly. Subcutaneous Implantation- Implant one 25mg pellet and repeat when necessary.

**Senile Vaginitis; Pruritis Vulvae; Kraurosis Vulvae:** -1.0 to 1.5mg of estradiol or 1.0 to 1.66mg of estradiol benzoate intramuscularly three times weekly for two or three injections, then 0.5 to 1.0mg of estradiol or 0.33 to 1.0mg of estradiol benzoate twice weekly for maintenance.

The pellets may be implanted conveniently and quickly by means of an injector or they may be administered by making an incision in the skin. Either method, though readily carried out in the physician's office, is a minor surgical procedure, and all aseptic precautions must be observed.

**BY INJECTOR:** The pellet may be quickly and easily implanted by means of the Bardani or Bartor Pellet Injectors. The areas usually selected for implantation are the intrascapular region or the posterior axillary line. Aseptic precautions must be observed for any surgical procedure. The skin is carefully cleaned, followed by the application of iodine and alcohol. The area is infiltrated with procaine 1:100. Make a very small incision (about 2mm long and 1mm deep) into the skin with a sharp scalpel to allow free passage of the large injector needle. The injector needle of the Kearns injector, with sharp plunger in place, is inserted into the incision and gently forced into the subcutaneous tissue at the desired site of implantation. The sharp plunger is withdrawn, and the pellet inserted into the hollow needle. The simplest method for placing the pellet in the needle is to allow the pellet to slide from the vial in which it is packed into the slot provided in the needle. The pellet is pushed as far as possible through the needle by means of the blunt plunger and held in place with the plunger while the needle is gently withdrawn. When the needle comes in contact with the knob of the plunger, both are withdrawn together. When the injector has been withdrawn, the wound may be closed with a single stitch or a skin clip. In many instances, apposition of the edges of the wound with adhesive tape is sufficient.

**BY INCISION:** The intrascapular region or the posterior axillary line are convenient sites for implanting pellets. The operative field is prepared in the usual manner with iodine and alcohol and the area is infiltrated with procaine 1:100 solution. An incision about 1 centimeter in length is made. With blunt dissection, a pocket about two centimeters in depth is prepared in the subcutaneous tissue below and away from the incision. The edges of the pocket may be held apart by a small dilator and the pellet inserted into the bottom of the pocket with small forceps. Force should not be used when inserting pellets. The incision is closed with one or two sutures.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or

recurring abnormal vaginal bleeding.

### **PACKAGING:**

Vial of one 25mg, pellet, box of 3; 10; 100

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#### ADVANCED PHARMACEUTICAL TECHNOLOGY

132 South Central Avenue, Elmsford, NY 10523

**Estra-50 (57377-050-01)**

FLUTED PARTITION 850 Union Avenue, Bridgeport, CT 06607 • 203-368-2548

Product: <u>ESTRA 50 MG</u>	Colors: <u>2</u>
Order No: _____ Date: <u>10/21/2019</u>	 <u>199C RED</u>
Size: <u>2.375 X .625 X 5.1875</u>	 <u>BLACK</u>
Description: <u>STRAIGHT TUCK</u>	
Material: <u>.016 SBS</u>	
Version No: _____ Approval: _____	

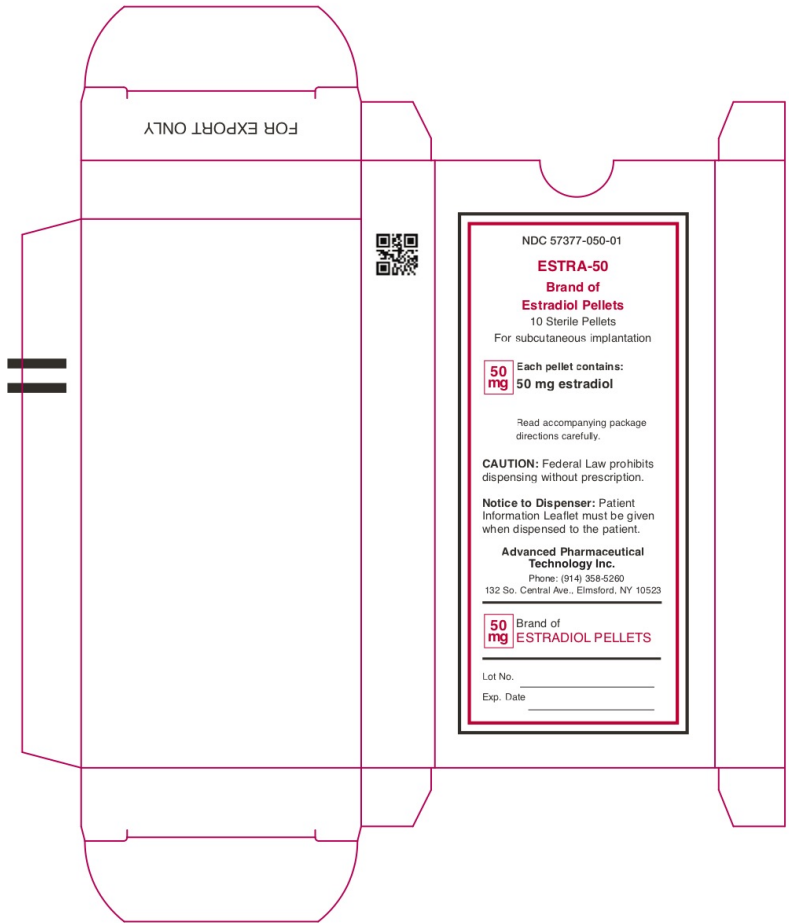
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**Estra-25 (57377-025-01)**

FLUTED PARTITION 850 Union Avenue, Bridgeport, CT 06607 • 203-368-2548

Product: <u>ESTRA 25 MG</u>	Colors: <u>2</u>
Order No: _____ Date: <u>10/21/2019</u>	 <u>199C RED</u>
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Material: <u>016 SBS</u>	<input type="checkbox"/>
Version No: _____ Approval: _____	<input type="checkbox"/>

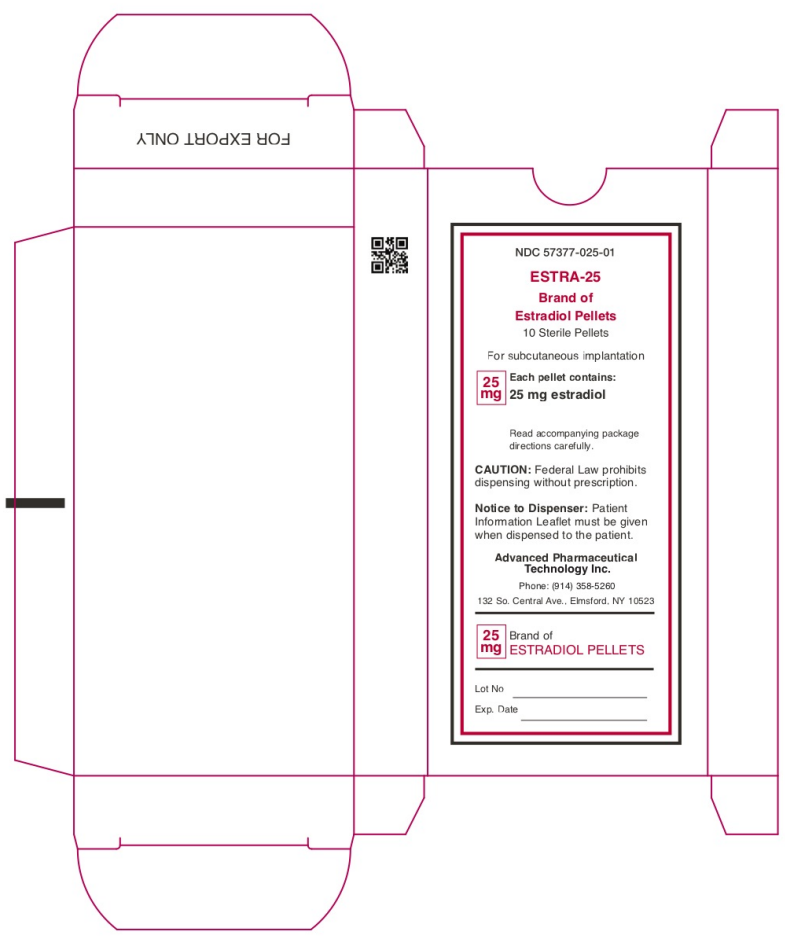
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<b>ESTRA-50</b>			
estradiol pellet pellet, implantable			
<b>Product Information</b>			
<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:57377-050
<b>Route of Administration</b>	SUBCUTANEOUS		
<b>Active Ingredient/Active Moiety</b>			
	<b>Ingredient Name</b>	<b>Basis of Strength</b>	<b>Strength</b>
	ESTRADIOL (UNII: 4TI98Z838E) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL	50 mg

## Inactive Ingredients

Ingredient Name	Strength
STEARIC ACID (UNII: 4ELV7Z65AP)	
POVIDONE (UNII: FZ989GH94E)	

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:57377-050-01	10 in 1 AMPULE; Type 0: Not a Combination Product	01/01/2017	

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
Export only		01/01/2017	

## ESTRA-25

estradiol pellet pellet, implantable

## Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:57377-025
Route of Administration	SUBCUTANEOUS		

## Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ESTRADIOL (UNII: 4T198Z838E) (ESTRADIOL - UNII:4T198Z838E)	ESTRADIOL	25 mg

## Inactive Ingredients

Ingredient Name	Strength
STEARIC ACID (UNII: 4ELV7Z65AP)	
POVIDONE (UNII: FZ989GH94E)	

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Export only		01/01/2017	

**Labeler** - Advanced Pharmaceutical Technology, Inc. (023237884)

**Establishment**

Name	Address	ID/FEI	Business Operations
Advanced Pharmaceutical Technology, Inc.		023237884	manufacture(57377-050, 57377-025)

Revised: 2/2020

Advanced Pharmaceutical Technology, Inc.