



独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

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Summary of Investigation Results

Estradiol (oral dosage form)

Estradiol valerate

Estriol (oral dosage form)

Progesterone (oral dosage form)

Estradiol/Norethisterone acetate

Estradiol/Levonorgestrel

Testosterone enanthate/Estradiol valerate

Estradiol (preparations for cutaneous application)

Estrogens, conjugated

October 22, 2025

Non-proprietary name

See attachment.

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Brand name (marketing authorization holder)

See attachment.

Japanese market launch

See attachment.

Indications

See attachment.

Summary of revisions

(1) to (10), (13) to (15)

1. The necessity of adding a precaution concerning breast cancer associated with the single-agent use of estrogen preparations to the section "8. IMPORTANT PRECAUTIONS" was discussed.
2. The results of overseas epidemiological studies will be added to the section "15.1 Information Based on Clinical Use" in "15. OTHER PRECAUTIONS."

(11) (12)

1. The necessity of adding a precaution concerning breast cancer associated with the single-agent use of estrogen preparations to the section "8. IMPORTANT PRECAUTIONS" was discussed.
2. The necessity of adding the results of overseas epidemiological studies to the section "15.1 Information Based on Clinical Use" in

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"15. OTHER PRECAUTIONS" was examined.

Investigation results and background of the revision

As a result of consultation with expert advisors regarding the necessity of revision of the Precautions, a causal relationship between hormone replacement therapy and breast cancer in menopausal women was not clear. However, based on the following points, it was judged appropriate to revise the section "15.1 Information Based on Clinical Use" in "15. OTHER PRECAUTIONS," instead of the section "8. IMPORTANT PRECAUTIONS," for preparations used for hormone replacement therapy in menopausal women, except for (11) and (12).

- In the results of WHI, a randomized clinical study in the US (JAMA 2006; 295: 1647-57), an association between conjugated estrogens and an increased risk of breast cancer has not been reported, and the presence or absence of a risk of breast cancer associated with estrogen monotherapy is not clear.
- Japanese and overseas guidelines state that the effect of hormone replacement therapy on the risk of breast cancer is small or absent.
- In a meta-analysis of large-scale overseas epidemiological studies (Lancet. 2019; 394: 1159-1168), all menopausal hormone replacement therapies except vaginal preparations were associated with an increased risk of breast cancer. The risk of breast cancer increased with longer duration of use and persisted in past users depending on the past administration period, even after discontinuation of administration.

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Attachment

No.	Non-proprietary name	Brand name	Marketing authorization holder	Japanese market launch	Indications
(1)	Estradiol	Estrana Tapes 0.09 mg, Estrana Tapes 0.18 mg, Estrana Tapes 0.36 mg, Estrana Tapes 0.72 mg	Hisamitsu Pharmaceutical Co., Inc.	0.09 mg, 0.18 mg, 0.36 mg: September 2015 0.72mg: February 2000	<Common to all drug products> ○ The following symptoms associated with climacteric disturbance and ovarian deficiency symptoms Vasomotor nerve symptoms (hot flush and sweating), genitourinary atrophic symptoms ○ Osteoporosis postmenopausal ○ Hypo-oestrogenism due to hypogonadism, gonadectomy or primary ovarian failure <Estrana Tapes 0.72 mg> ○ Adjustment of the timing of initiation of controlled ovarian stimulation in assisted reproductive technology <Estrana Tapes 0.36 mg, Estrana Tapes 0.72 mg>

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					○ Hormone replacement cycle in frozen and thawed embryo transfer
(2)		Julina tablets 0.5 mg, etc.	Bayer Yakuhin, Ltd., etc.	September 2008	○ The following symptoms associated with climacteric disturbance and ovarian deficiency symptoms - Vasomotor nerve symptoms (hot flush and sweating), vaginal atrophic symptoms ○ Osteoporosis postmenopausal ○ Adjustment of the timing of initiation of controlled ovarian stimulation in assisted reproductive technology ○ Hormone replacement cycle in frozen and thawed embryo transfer
(3)		Divigel 1 mg	Orion Pharma Japan K.K.	November 2007	○ Vasomotor nerve symptoms associated with climacteric disturbance and ovarian deficiency symptoms (hot flush and sweating) ○ Adjustment of the timing of initiation of controlled ovarian stimulation in assisted reproductive technology



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					○ Hormone replacement cycle in frozen and thawed embryo transfer
(4)		L'estrogeol 0.06%	Fuji Pharma Co., Ltd.	August 2007	○ Vasomotor nerve symptoms associated with climacteric disturbance and ovarian deficiency symptoms (hot flush and sweating) ○ Adjustment of the timing of initiation of controlled ovarian stimulation in assisted reproductive technology ○ Hormone replacement cycle in frozen and thawed embryo transfer
(5)	Estradiol valerate	Progynon-Depot intramuscular injection 10 mg	Fuji Pharma Co., Ltd.	September 1956	Amenorrhea, menstrual cycle abnormal (oligomenorrhea and hypermenorrhea), menstrual volume abnormal (hypomenorrhoea and menorrhagia), dysmenorrhea, functional uterine haemorrhage, uterine hypoplasia, ovarian deficiency symptoms, climacteric disturbance, infertility
(6)		Pelanin depot Intramuscular Injection 5 mg, 10 mg	Mochida Pharmaceutical Co., Ltd.	5mg: August 1956 10 mg: November 1954	Amenorrhea, menstrual cycle abnormal (oligomenorrhea and hypermenorrhea), menstrual volume abnormal (hypomenorrhoea and menorrhagia), dysmenorrhea, functional uterine haemorrhage,



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					uterine hypoplasia, ovarian deficiency symptoms, climacteric disturbance, infertility
(7)	Estradiol/Norethisterone acetate	Menoaidcombi Patches	Hisamitsu Pharmaceutical Co., Inc.	February 2009	Vasomotor nerve symptoms associated with climacteric disturbance and ovarian deficiency symptoms (hot flush and sweating)
(8)	Estradiol/Levonorgestrel	Wellnara combination tablets	Bayer Yakuhin, Ltd.	February 2009	Osteoporosis postmenopausal
(9)	Estriol	Estriol Tablets 100 μ , 0.5 mg, 1 mg, etc.	Mochida Pharmaceutical Co., Ltd., etc.	100 μ : November 1960 0.5 mg: August 1984 1 mg: August 1969	<Common to all drug products> Climacteric disturbance, vaginitis (senile, pediatric, and nonspecific), cervicitis, and cervicovaginal erosion <0.5 mg tablet, 1 mg tablet> Senile osteoporosis
(10)		Holin Tablets 1 mg	Aska Pharmaceutical Co., Ltd.	April 1973	Climacteric disturbance, vaginitis (senile, pediatric, and nonspecific), cervicitis, and cervicovaginal erosion, senile osteoporosis
(11)	Estriol	Estriol Vaginal Tablets 0.5 mg	Mochida Pharmaceutical Co., Ltd.	September 1961	Vaginitis (senile, pediatric, and nonspecific), cervicitis, and cervicovaginal erosion
(12)		Holin V Vaginal Tablets 1 mg	Aska Pharmaceutical Co., Ltd.	June 1962	Vaginitis (senile, pediatric, and nonspecific), cervicitis, and cervicovaginal erosion
(13)	Estrogens, conjugated	Premarin Tablets 0.625 mg	Pfizer Japan Inc.	August 1999	Ovarian deficiency symptoms, ovarian failure, climacteric disturbance,



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					vaginitis (senile, pediatric, and nonspecific), and functional uterine haemorrhage
(14)	Testosterone enanthate/Estradiol valerate	Primodian-Depot intramuscular injection, etc.	Fuji Pharma Co., Ltd., etc.	September 1956	Climacteric disturbance, ovarian deficiency symptoms, osteoporosis
(15)	Progesterone	F-meno capsules 100 mg	Fuji Pharma Co., Ltd.	November 2021	Suppression of the onset of endometrial hyperplasia during treatment with estrogen for climacteric disturbance and ovarian deficiency symptoms

The expert advisors present at the Expert Discussion regarding the current investigation were nominated based on their conflict of interest declarations concerning the relevant products, pursuant to the “Rules for Convening Expert Discussions, etc.”, by the Pharmaceuticals and Medical Devices Agency” (PMDA Administrative Rule No. 20-8, dated December 25, 2008).

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