- Oral contraceptive -

**ANGE® 21 TABLETS**

**ANGE® 28 TABLETS**

<Levonorgestrel and Ethinylestradiol Tablets>

prescription-only drug

<table>
<thead>
<tr>
<th>Storage</th>
<th>ANGE 21 TABLETS</th>
<th>ANGE 28 TABLETS</th>
</tr>
</thead>
<tbody>
<tr>
<td>The product should be stored at room temperature.</td>
<td>22100AMX01782</td>
<td>22100AMX01783</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Expiration date</th>
<th>Use before the expiration date indicated on the package.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval No.</td>
<td>22100AMX01782</td>
</tr>
<tr>
<td>Date of listing in the NHI reimbursement price</td>
<td>Not listed</td>
</tr>
<tr>
<td>Date of initial marketing in Japan</td>
<td>April 2002</td>
</tr>
</tbody>
</table>

**CAUTION**

Use only pursuant to the prescription of a physician.

**Patients or women shall be advised that oral contraceptives do not prevent infections of HIV (AIDS) or other sexually transmitted diseases (e.g., syphilis, genital herpes, gonorrhea, chlamydia infection, condyloma acumina, vaginal trichomoniasis, hepatitis B, etc.) and that the use of condoms is effective for the prevention of the above diseases. If necessary, tests for sexually transmitted disease shall be considered.**

**CONTRAINDICATIONS (ANGE is contraindicated in the following patients or women.)**

1. Women having hypersensitivity to the active ingredients of this drug.
2. Patients known or suspected estrogen-dependent tumor (e.g., breast cancer, cancer of uterine body, uterine myoma) or cervical cancer.
   [Tumor may be aggravated or may be actualized.]
3. Patients with undiagnosed abnormal genital bleeding.
   [Genital cancer may be suspected. In case that the bleeding is due to genital cancer, cancer may be aggravated or may be actualized.]
4. Patients with or having history of thrombophlebitis, pulmonary embolism, cerebrovascular disorder or coronary artery disease.
   [Blood coagulation may increase, and these symptoms may be aggravated.]
5. Women of 35 years old or over and consuming 15 or more cigarettes per day. [It is reported that cardiovascular disorder such as myocardial infarction, etc., may be induced.]
6. Migraine patients with aura (scintillating scotoma, astral flash, etc.). [It is reported that cerebrovascular disorders (apoplexy, etc.) may be induced in migraine patients with aura more than in migraine patients without aura.]
7. Valvular heart disease patients concurrent with pulmonary hypertension or auricular fibrillation and valvular heart disease patients with a history of subacute bacterial endocarditis.
   [It is reported that cardiovascular disorder such as thrombosis, etc., may be induced.]
8. Diabetes mellitus patients with vascular lesion (diabetic nephropathy, retinopathy, etc.)
   [It is reported that cardiovascular disorder such as thrombosis, etc., may be induced.]
   [It is reported that cardiovascular disorder such as thrombosis, etc., may be induced.]
10. Patients with antiphospholipid antibody syndrome
    [It is reported that cardiovascular disorder such as thrombosis, etc., may be induced.]
11. Patients within 4 weeks before surgery, within 2 weeks after surgery, within 4 weeks after delivery and who are in resting state for a long time.
    [Blood coagulability may be elevated, and risk of cardiovascular adverse reactions may be increased.]
12. Patients with severe hepatic disorder
    [Symptoms may be aggravated due to decreased metabolic functions and increased load to the liver.]
13. Patients with hepatic tumor. [Symptoms may be aggravated.]
14. Patients with abnormal lipid metabolism. [It is reported that cardiovascular disorders such as thrombosis, etc.,
may be induced. Since the drug may affect the lipid metabolism, the symptoms may be aggravated.

15. Patients with hypertension (excluding mild hypertension) [It is reported that cardiovascular disorders such as thrombosis, etc., may be induced. Symptoms may be aggravated.]

16. Patients with otosclerosis (a form of hearing loss) [Symptoms may be aggravated.]

17. Patients with history of jaundice, continuous pruritus, herpes gestations during the pervious pregnancy. [Symptoms may be recurred.]

18. Women known or suspected pregnancy. (refer to "Use during Pregnancy or Lactation")

19. Women in the lactating period (refer to "Use during Pregnancy or Lactation")

20. Women before puberty. [Early epiphyseal closing may be induced.]

INDICATIONS
Contraception (prevention of pregnancy)

<Precautions for use relating to indications>
- It is reported that the failure rate in the use of oral contraceptives for 1-year period (including missing pills) is 8%. [refer to "CLINICAL STUDIES"]

DOSAGE AND ADMINISTRATION
ANGE 21 TABLETS:
In the 1st cycle, one red-brown tablet, is orally administered once a day at the same time of the day. Then white tablet and yellow tablet are orally administered in the same manner in accordance with designated order (total: 21 days), and the drug is discontinued for 7 days.

In the 2nd cycle, one red-brown tablet is orally administered in the same manner on the 29th day after the start of administration of the 1st cycle, and the drug is discontinued for 7 days. In the 3rd cycle and thereafter, the drug is administered in the same manner as in the 2nd cycle.

ANGE 28 TABLETS:
In the 1st cycle, one red-brown tablet, is orally administered once a day at the same time of the day. Then white tablet, yellow tablet and red tablet are orally administered in the same manner in accordance with designated order (total: 28 days).

In the 2nd cycle, one red-brown tablet is orally administered in the same manner on the 29th day after the start of administration of the 1st cycle. In the 3rd cycle and thereafter, the drug is administered in the same manner as in the 2nd cycle.

<br><br><br>

PRECAUTIONS
1. Careful Administration (ANGE should be administered with care in the following patients or women.)

(1) Women at the age of 40 years or older [The incidence of cardiovascular disorder such as myocardial infarction, etc., is apt to occur in such age, and the drug may promote the incidence.]

(2) Women having family history of breast cancer or having breast induration [Since some reports suggest the relationship between estrogen administration and occurrence of breast cancer, the drug shall be administered carefully with periodic examination of breast, etc.]

(3) Smokers (refer to "CONTRAINDICATIONS")

(4) Women with obesity [It is reported that cardiovascular disorders such as thrombosis, etc., may be induced.]

<br><br><br>
2. Important Basic Precautions

(1) Since the administration of this drug may cause thrombosis, the administration shall be discontinued in case that the following symptoms or condition occur. Also women shall be advised beforehand that they shall consult physicians, etc., in case that such symptoms or condition are observed.

1) Initial symptoms of thrombosis
   - Pain or edema of lower extremities, sudden shortness of breath, chest pain, severe headache, acute visual disturbance, etc.
   - Condition at which the risk of thrombosis is increased, immobilized condition, obvious elevation of blood pressure, etc.

(2) It is reported that the risk of serious adverse reactions in cardiovascular systems may be increased by smoking. Therefore women shall be advised to stop smoking. (refer to "CONTRAINDICATIONS")

(3) Prior to the administration, confirm sufficiently that the women are not pregnant by inquiry, vaginal examination, measurement of basal body temperature, immunological diagnosis of pregnancy, etc.

(4) A surveillance of the history of disease and medical examination of the women is necessary. The medical check will include measurement of blood pressure, examination of breast and abdomen and clinical laboratory test.

(5) In case of administration for a long time, consider the medical check in every 6-months period and examination of pelvic viscera such as uterus and ovary (especially, cytologic diagnosis of uterine cervix) every year.

(6) Advise women to make a self check of breast. Especially in case that they have a family history of breast cancer or breast induration.

(7) Advise women the administration method sufficiently not to forget taking drugs. In case of missing drugs (excluding red tablets), if they notice it by next day, administer the missed drug immediately and continue the drug of the day as usual.

In case of missing drugs for 2 or more consecutive days, discontinue the administration and wait for next menstrual cycle, and resume the administration. Since the possibility of pregnancy is increased by missing drugs, other forms of contraception shall be employed in such cycle.

(8) Although an irregular bleeding which appears during administration usually disappear in the course of administration, if it persists for a long time, cytologic diagnosis of vagina, etc., shall be conducted in order to confirm that it is not attributable to malignant diseases prior to continuation of administration.

(9) In case that severe diarrhea or vomitting is continued during administration period, insufficient absorption of the drug may be induced, and possibility of pregnancy may be increased. In such case, other forms of contraception shall be also employed in such cycle.

(10) In case of the absence of withdrawal bleeding for 2 consecutive cycles, confirm the absence of pregnancy prior to continuation of administration.

(11) It is advisable to continue the contraception until women show regular menstrual cycle if they stop taking the drug and desire pregnancy.

(12) Switch from other brands of oral contraceptives

1) From 21 tablet-products
   - All tablets of previous product shall be administered, and, after 7 days' break, this drug shall be started. If the administration of this drug delays, women may become pregnant.

2) From 28 tablet-products
   - All tablets of previous product shall be administered, and continuously this drug shall be started. If the administration of this drug delays, women may become pregnant.

3. Drug Interactions

[Precautions for coadministration] (ANGE should be administered with care when coadministered with the following drugs.)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Signs, Symptoms and Treatment</th>
<th>Mechanism and Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal hormones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone, etc.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricyclic antidepressant drugs</td>
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<td></td>
</tr>
<tr>
<td>Imipramine, etc.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selegiline</td>
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<td></td>
</tr>
<tr>
<td>Hydrochloride Ciclosporin</td>
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</tr>
</tbody>
</table>

It is considered that ANGE inhibits the metabolism of these drugs.
4. Adverse Reactions

Clinical trials were conducted in 731 cases in Japan, and 690 cases (9,638 cycles) were investigated. Adverse reaction rate was 29.4% (203 cases), and main adverse reactions were gastrointestinal symptoms (17.5%), uterine or breast symptoms (7.8%), headache (7.8%), etc. (as of the approval). Clinical trials were conducted in 731 cases in Japan, and 690 cases (9,638 cycles) were investigated. Adverse reactions were gastrointestinal symptoms (17.5%), uterine or breast symptoms (7.8%), headache (7.8%), etc. (as of the approval). Adverse reactions were gastrointestinal symptoms (17.5%), uterine or breast symptoms (7.8%), headache (7.8%), etc. (as of the approval).

4.1 Clinically significant adverse reactions

Thrombosis: Thrombosis (extremities, lung, myocardium, brain, retina, etc.) (incidence unknown) may occur. Sufficient care shall be taken, and, in case that initial symptoms, such as pain or edema in lower extremities, sudden shortness of breath, chest pain, severe headache, acute visual disturbance, etc., occur, discontinue the administration of the drug and take appropriate measures.

4.2 Other adverse reactions

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥5%</td>
<td>Rash, etc.</td>
</tr>
<tr>
<td>5% &gt; 0.1%</td>
<td>Visual disturbance due to retinal vascular disorder</td>
</tr>
<tr>
<td></td>
<td>Abnormal hepatic function</td>
</tr>
<tr>
<td></td>
<td>Jaundice, etc.</td>
</tr>
<tr>
<td></td>
<td>Edema, weight increase</td>
</tr>
<tr>
<td></td>
<td>Change in the amount of menstrual bleeding, vaginal candidiasis, etc.</td>
</tr>
<tr>
<td></td>
<td>Lactation, mastalgia, breast swelling, breast atrophy, breast enlargement</td>
</tr>
<tr>
<td></td>
<td>Increased blood pressure, heart pounding, etc.</td>
</tr>
<tr>
<td></td>
<td>Thirst, stomatitis, abdominal pain, bulimia, etc.</td>
</tr>
<tr>
<td></td>
<td>Depression, etc.</td>
</tr>
<tr>
<td></td>
<td>Pigmentation, etc.</td>
</tr>
<tr>
<td></td>
<td>Coldness, numbness, compensatory epistaxis, feeling of warmth, total cholesterol increased, triglyceride increased, etc.</td>
</tr>
</tbody>
</table>

[Note]

1) In such cases, the administration of the drug should be discontinued.
2) In such cases, appropriate measures, such as discontinuation of the drug, etc., should be taken.
3) Care should be taken not to be exposed to sunshine for a long time.

5. Use during Pregnancy or Lactation

(1) The drug should be discontinued in case that pregnancy is confirmed. In case that women have no withdrawal bleeding for 2 consecutive cycles, they may be
pregnant, and should be confirmed whether they are pregnant or not.
[Safety during pregnancy has not been established.]
(2) To nursing mothers, proper advice such as choosing other forms of contraception should be given.
[Fall in the quality and quantity of breast milk may occur. It is reported that excretion of the drug in breast milk, jaundice in neonates and breast enlargement are observed.]

6. Effects on Clinical Laboratory Test
Increase in total cortisol, total T3, total T4 may be observed due to increase in serum proteins (corticoid-binding globulin, thyroxin-binding globulin, etc.) induced by ethinylestradiol contained in the drug. However, it is reported that free-type of these items do not change. Care should be taken in the judgment of these clinical laboratory test values.

7. Precautions concerning Use
At dispensing drugs
For drugs that are dispensed in a press-through package (PTP), instruct the patient to remove the drug from the package prior to use. (It has been reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, resulting in severe complications such as mediastinitis.)

8. Other Precautions
(1) The results of foreign epidemiological survey report that the risk of venous thrombosis of women taking oral contraceptives is 3.25 to 4.0 times as high as that of women who do not take oral contraceptives. Also, it is reported that the risk of venous thrombosis becomes the highest during the first year of the use of oral contraceptives.

(2) The results of foreign epidemiological survey report that the risk of breast cancer and cervical cancer become high by taking oral contraceptives.

(3) It is reported that in foreign countries the use of oral contraceptives for 2 years or longer gives the occurrence of benign hepatic tumor in 3.4 cases per 100,000 users. Also intraperitoneal bleeding due to rupture of tumor may occur. On the other hand, the incidence of malignant hepatic tumor (hepatic cancer) is very low, which is less than 1 case per 1,000,000 users.

(4) It is reported that when estrogens are administered to pregnant animals (mice), malignant degeneration in vaginal epithelial tissue and endometrium of grown-up animals is suggested. It is reported that when estrogens are administered to newborn animals (mice), malignant degeneration in vaginal epithelial tissue of grown-up animals is observed.

(5) It is reported that in foreign countries the use of oral contraceptives caused the aggravation of systemic lupus erythematosus (SLE), anaphylactoid reaction and haemolytic-uraemic syndrome (HUS) are observed.

(6) It is reported that in foreign countries the use of oral contraceptives caused the changes in vision and visual field, discomfort of wearing contact lenses, etc., due to the difficulty in the adjustment of contact lenses caused by the change in the thickness of cornea, etc.

PHARMACOKINETICS
When one tablet of each phase of the drug was orally administered to healthy adult women, levonorgestrel and ethinylestradiol were quickly absorbed and reached the maximum plasma concentration (Cmax) at 1 to 1.5 hours, and then decreased with dual phase pattern thereafter. The half life at the final phase was: levonorgestrel: 10 to 26 hours, ethinylestradiol: 4 to 8 hours. Regardless the ratio of levonorgestrel and ethinylestradiol, the Cmax and area under concentration-time curve (AUC) were dose-dependent, in general.

When the drug was administered to healthy adult women for 1 cycle (21 days), plasma concentration of levonorgestrel is higher than that estimated by the results of single dose administration, which is considered to be due to the effect of sexual hormone binding globulin induced by ethinylestradiol administration. No changes in pharmacokinetics of ethinylestradiol by repeated administration were observed, and the course was same as that of single administration.

CLINICAL STUDIES
In the Phase III clinical trials conducted in Japan, total number of cases to which the drug was administered was 731 cases, and 690 cases (9,638 cycles) were subject to the investigation. Of 676 cases (9,375 cycles), 2 pregnancy cases were observed, and 690 cases (9,638 cycles) were subject to the investigation. In the Phase III clinical trials conducted in Japan, total number of cases to which the drug was administered was 731 cases, and 690 cases (9,638 cycles) were subject to the investigation. Of 676 cases (9,375 cycles), 2 pregnancy cases were observed, and Pearl Index was 0.28.

Percentage of women experiencing an unintended pregnancy during the first year of typical use and the first year of perfect use of contraception

<table>
<thead>
<tr>
<th>Method</th>
<th>Perfect use* (%)</th>
<th>Typical use** (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral contraceptives</td>
<td>0.3</td>
<td>8</td>
</tr>
<tr>
<td>Spermicides</td>
<td>18</td>
<td>29</td>
</tr>
<tr>
<td>(Foams, gels***, creams ***)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IUD (drugs added)</td>
<td>0.1-0.6</td>
<td>0.1-0.8</td>
</tr>
<tr>
<td>Condom</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Diaphragm (pessary)</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>Periodic abstinence</td>
<td>1.9</td>
<td>25</td>
</tr>
<tr>
<td>Female sterilization</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Male sterilization</td>
<td>0.10</td>
<td>0.15</td>
</tr>
<tr>
<td>Without contraception</td>
<td>85</td>
<td>85</td>
</tr>
</tbody>
</table>

*: Among couples who use the method perfectly (both consistently and correctly), the percentage who experience an accidental pregnancy.

**: Among couples, the percentage who experience an accidental pregnancy (in case of oral contraceptives, the rate including missing drugs).

***: Not marketed in Japan
PHARMACOLOGY

Major action of this drug is suppression of ovulation due to inhibition of LH and FSH secretion from the pituitary gland. In addition, inhibition of implantation by changing endometrium and inhibition of migration of sperm by changing cervical mucus are also added to show the contraceptive effects.

PHYSICOCHEMISTRY

Nonproprietary name:

Levonorgestrel [JAN]

Chemical name:

18α-Homo-19-nor-17β-hydroxy-17α-pregn-4-en-20-yn-3-one

Molecular formula:

C_{21}H_{28}O_{2}

Structural formula:

![Structural formula of Levonorgestrel]

Molecular weight: 312.45

Melting point: 234-240°C

Description:

Levonorgestrel occurs as white crystals or crystalline powder. It is odorless. It is soluble in tetrahydrofuran and in chloroform, slightly soluble in methanol, in ethanol (99.5), in acetonitrile and in ether, and practically insoluble in water.

Nonproprietary name:

Ethinylestradiol [JAN]

Chemical name:

17α-Ethynylestra-1,3,5(10)-triene-3,17β-diol

Molecular formula:

C_{20}H_{24}O_{2}

Structural formula:

![Structural formula of Ethinylestradiol]

Molecular weight: 296.40

Melting point: 180-186°C or 142-146°C

Description:

Ethinylestradiol occurs as white to pale yellow crystals or crystalline powder. It is odorless. It is freely soluble in pyridine and in tetrahydrofuran, soluble in ethanol (95) and in diethyl ether, and practically insoluble in water. It dissolves in sodium hydroxide TS.

PACKAGING

ANGE 21 TABLETS:

- Boxes of 252 tablets (21 tab. × 12)
- Boxes of 1,260 tablets (21 tab. × 60)

ANGE 28 TABLETS:

- Boxes of 84 tablets (28 tab. × 3)
- Boxes of 336 tablets (28 tab. × 12)
- Boxes of 1,680 tablets (28 tab. × 60)

REFERENCES

<MAJOR LITERATURES>

4) In-house documents (Influence on rat reproductive function of levonorgestrel)
5) In-house documents (Preclinical genital pharmacodynamics)

<REFERENCE INFORMATION>

I. Safety

1. Matters concerning tumors
   • WHO: Int. J. Cancer, 55: 228-236, 1993
   • Thomas, DB et al.: Am. J. Epidemiol., 144 : 281-289, 1996
   • Principle Gynecology & Obstetrics - Gynegology, p. 618-623, Medical View Co.Ltd.,1987
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2. Matters concerning cardiovascular system

- Bour, J. et al.: Teratology, 12: 11-26, 1975
- Matsunaga, H.: Sanfujinka Chiryo (Obstetrical and Gynecological Therapy), 32: 88-93, 1976

3. Matters concerning next generations

- Morii, T.: Igaku no Ayumi, 95: 599-602, 1975
- Surveillance of congenital anomaly for 20 years: Japan Association of Obstetricians & Gynecologists, 1993
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- Matsunaga, H.: Sanfujinka Chiryo (Obstetrical and Gynecological Therapy), 32: 88-93, 1976

4. Matters concerning fertility

II. Efficacy

1. Matters concerning contraception effect


2. Information on artificial interruption of pregnancy

- Report of public opinion for family planning (23rd) (Surveillance Group for Population Matters, Mainichi Newspaper)
- Determinants of contraceptive use

3. Information on other effects

- The Centers for Disease Control Cancer and Steroid Hormone Study: JAMA, 249: 1596-1599, 1983
- The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development: JAMA, 257: 796-800, 1987
- Royal College of General Practitioners: Oral contraceptives and health, p. 22, p. 61, Pitman Medical, London, 1974

REQUEST FOR LITERATURE AND INQUIRIES
OF PRODUCT INFORMATION SHOULD BE MADE TO:
Drug Information Unit
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FAX 03-5484-8358

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