**Premarin®** (conjugated estrogens)

**0.3mg Tablets**

**DESCRIPTION**
PREMARIN® (conjugated estrogens tablets) for oral administration contains a mixture of conjugated estrogens obtained exclusively from natural sources.

**INDICATIONS**
Treatment of moderate to severe vasomotor symptoms associated with the menopause.

- Treatment of vulvar and vaginal atrophy. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
- Prevention of postmenopausal osteoporosis.
- Prevention of postmenopausal osteoporosis in women at risk of future fractures. Therapy should start as soon as possible after the onset of menopause.
- Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.
- Treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
- Treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only).

**DOSAGE AND ADMINISTRATION**
Patients should be reevaluated periodically to determine if treatment for symptoms is still necessary.

- If an estrogen is prescribed for a postmenopausal woman with a uterus, the addition of a progestin may be appropriate (see section, Malignant neoplasms). In some cases, hysterectomized women with a history of endometriosis may need a progestin (see Section, Exacerbation of other conditions).
- Tablets should be taken whole; do not divide, crush, chew, or dissolve tablets in mouth.
- Dosage adjustment may be made based on individual patient response.
- Vasomotor Symptoms and/or Vulvar and Vaginal Atrophy
  - Consider topical vaginal products when treating solely for vulvar and vaginal atrophy.
- Prevention of postmenopausal osteoporosis
  - Therapy should be considered for postmenopausal women at risk of future fractures and should start as soon as possible after the onset of menopause.
- Female hypogonadism
  - Administer cyclically (e.g., three weeks on and one week off).
- Female castration or primary ovarian failure
  - Administer cyclically (e.g., three weeks on and one week off).
- Breast cancer (for palliation only)
  - 10mg three times daily, for a period of at least three months.
- Advanced androgen-dependent carcinomas of the prostate (for palliation only)
  - 1.25mg to 2.5 mg three times daily.

**CONTRAINDICATIONS**
- Known or suspected pregnancy (see section, pregnancy).
- Undiagnosed abnormal uterine bleeding.
- Known, suspected, or past breast cancer (except use of tablets in appropriately selected patients being treated for metastatic disease).
- Known or suspected estrogen-dependent neoplasia (e.g., endometrial cancer, endometrial hyperplasia).
- Active or history of arterial thromboembolic disease (e.g., stroke, myocardial infarction) or venous thromboembolism (such as deep vein thrombosis, pulmonary embolism).
- Active or chronic liver dysfunction or disease.
- Known or suspected hypersensitivity to ingredients.

**SPECIAL WARNINGS**

**General**
Combined Estrogen and Progestin Therapy:
There are additional and/or increased risks that may be associated with the use of combination estrogen-plus-progestin therapy compared with using estrogen-alone regimens. These include an increased risk of myocardial infarction, pulmonary embolism, invasive breast cancer and ovarian cancer.

**Cardiovascular risk**
ERT has been reported to increase the risk of stroke and deep venous thrombosis (DVT).

- Patients who have risk factors for thrombotic disorders should be kept under careful observation.

**Stroke**
In the estrogen-alone substudy of the WHI, a statistically significant increased risk of stroke was reported in women receiving estrogen alone compared with women receiving placebo (45 vs. 33 per 10,000 person-years). The increase in risk was observed during year one and persisted. Should a stroke occur, the suspected estrogen should be discontinued immediately (see section, pharmacodynamics, clinical efficacy).

**Venous thromboembolism**
In the estrogen-alone substudy of WHI, the increased risk of deep venous thrombosis (DVT) was reported to be statistically significant (7.5 vs. 6.8 per 10,000 person-years). The risk of pulmonary embolism (PE) was reported to be increased, although it did not reach statistical significance. The increase in VTE (DVT and PE) risk was demonstrated during the first two years (30 vs. 22 per 10,000 person-years). Should a VTE occur, the suspected estrogen should be discontinued immediately (see section, pharmacodynamics, clinical efficacy).

If feasible, estrogens should be discontinued at least four to six weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

**Malignant neoplasms**

**Endometrial cancer**
The use of unopposed estrogens in women with an intact uterine cavity has been associated with an increased risk of endometrial cancer (see section, EXACERBATION OF OTHER CONDITIONS and section, pharmacodynamics, clinical efficacy).

The reported endometrial cancer risk among unopposed estrogen users is about 2- to 15-fold greater than in nonusers, and appears dependent on duration of treatment and on estrogen dose. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more, and this risk has been shown to persist for at least 8 to 15 years after ERT is discontinued. Adding a progestin to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer (see section, Malignant neoplasms).

Clinical surveillance of all women taking estrogen or estrogen-plus-progestin combinations is important. Adequate diagnostic measures should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal uterine bleeding.

**Breast cancer**
Studies involving the use of estrogens by postmenopausal women have reported inconsistent results on the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the Women's Health Initiative (WHI) Estrogen Plus Progestin, PHARMACODYNAMICS, EFFICACY). In the estrogen-alone substudy of WHI, after an average of 7.1 years of follow-up, CE (0.625 mg daily) was not associated with an increased risk of invasive breast cancer.

Some observational studies have reported an increased risk of breast cancer for estrogen-alone therapy after several years of use. The risk increased with duration of use, and appeared to return to baseline within approximately five years after stopping treatment (only the observational studies have substantial data on risk after stopping).

The use of estrogen has been reported to result in an increase in abnormal mammograms requiring further evaluation.

**Ovarian cancer**
In some epidemiologic studies, the use of estrogen-only preparations has been associated with an increased risk of ovarian cancer over multiple years of use. Other epidemiologic studies have not found these associations.

**Dementia**
A subsidiary of the Women's Health Initiative Memory Study.
(WHIMS), an ancillary study of WHI conducted in women aged 65-79, reported an increased risk of developing probable dementia when compared with placebo (see section, GERIATRIC USE, and section PHARMACODYNAMICS, CLINICAL EFFICACY).

**Gallbladder disease**
A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving ERT has been reported.

**Visual abnormalities**
Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.

**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.

**Palliative therapy in men**
Large doses of estrogen (5 mg conjugated equine estrogens per day), concomitant to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men of case reports to the risks of nondental myocardial infarction, pulmonary embolism, and thrombophlebitis.

**PRECAUTIONS**
**Fluid retention**
Because estrogens may cause some degree of fluid retention, patients with conditions which might be influenced by this factor, including cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

**Hypertriglyceridemia**
In the Health and Osteoporosis, Progestin and Estrogen (HOPE) study, the mean percent increases from baseline in serum triglycerides after one year of treatment with CE 0.625mg, 0.45mg, and 0.3mg compared with placebo were 34.3, 30.2, 26.1, and 10.7, respectively.

Caution should be exercised in patients with pre-existing hypertriglyceridemia since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen therapy in this population.

**History of cholestatic jaundice**
For patients with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

**Elevated blood pressure**
In a small number of case reports, substantial increases in blood pressure during ERT have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial a generalized effect of ERT on blood pressure was not seen.

**Exacerbation of other conditions**
Estrogen replacement therapy may cause an exacerbation of asthma, epilepsy, migraine, diabetes mellitus with or without vascular disease, treatment, polypharmacy, systemic lupus erythematosus, and hepatic hemangiomas, and should be used with caution in women with these conditions.

**Endometriosis**
may be exacerbated with administration of ERT. Addition of a progestin should be considered in women who have undergone hysterectomy but are known to have residual endometriosis, since malignant transformation after estrogen-only therapy has been reported.

**Hypocalcemia**
Estrogen use should be used with caution in individuals with disease that can predispose to severe hypocalcemia.

**Hypothyroidism**
Patients dependent on thyroid hormone replacement therapy may require increased doses in order to maintain their free thyroid hormone levels in an acceptable range (see section, Laboratory test interactions).

**Laboratory monitoring**
Estrogen administration should be guided by clinical response rather than by hormone levels (eg, estradiol, FSH).

**PREGNANCY**
Estrogens should not be used during pregnancy (see section, CONTRAINDICATIONS).

**LACTATION**
Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of breast milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving the drug. Caution should be exercised when estrogens are administered to a nursing woman.

**PEDIATRIC USE**
Clinical studies have not been conducted in the pediatric population. Although estrogen replacement therapy has been used for the induction of puberty in adolescents with some forms of pubertal delay; safety and effectiveness in pediatric patients have not been established. Estrogen treatment of prepubertal girls also induces premature breast development and vaginal cornification, and may induce uterine bleeding.

Since large and repeated doses of estrogen over an extended time period have been shown to accelerate epiphyseal closure, hormonal therapy should not be started before epiphyseal closure has occurred in order not to compromise final growth.

**GERIATRIC USE**
The estrogen-alone subset of the Women's Health Initiative (WHI) reported an increased risk of stroke compared with placebo in postmenopausal women 65 years of age or older (see section, Cardiovascular risk and section, Pharmacodynamics, clinical efficacy).

A subset of the Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI conducted in women aged 65-79, reported an increased risk of developing probable dementia when compared with placebo (see section, Dementia and section, pharmacodynamics, clinical efficacy).

**INTERACTIONS**
Data from a drug-drug interaction study involving conjugated estrogens and mesoridoxepropionate acetate indicate that the pharmacokinetic disposition of both drugs is not altered when the drugs are coadministered. Other clinical drug-drug interaction studies have not been conducted with conjugated estrogens.

In vitro and in vivo studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's Wort, St. John's Wort analogs (Hypericum perforatum), Phenoibarbitals, phenytoin, carbamazepine, rifampicin and dexamethasone may induce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4, such as cimetidine, disulfiram, etoposide, ketocazole, ritonavir, and troleandomycin, may increase plasma concentrations of estrogens and may result in side effects.

**INTERFERENCE WITH LABORATORY AND OTHER DIAGNOSTIC TESTS**
**Laboratory Test Interactions**
Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factor IX, VIII, IX, X, XII, VII-X complex, II-VII-X complex, and beta thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity/increased levels of fibrinogen and fibrinogen activity, increased plasminogen antigen and activity.

Estrogens 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 radiiocummonoassay or T3 levels by radiocolsummonoassay. 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., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroid and sex steroids, respectively. Free or biologically active hormone concentrations may be decreased. Other protein, plasmatic proteins, increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

Increased plasma HDL and HDL cholesterol subtraction concentrations, reduced LDL cholesterol concentrations, increased triglyceride levels.

Impaired glucose tolerance.

The response to metformin may be reduced.

**Adverse Reactions**

<table>
<thead>
<tr>
<th>Common Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Common</td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td>Very rare</td>
</tr>
</tbody>
</table>

**System Organ Class**

**Adverse Reaction**

<table>
<thead>
<tr>
<th>Reproductive system and breast disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td>Very rare</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>

**Gastrointestinal disorders**

| Uncommon | Nausea; bleeding; abdominal pain |
| Rare | Vomiting; pancreatitis; ischemic colitis |
Nervous system disorders
Uncommon Dizziness; headache; migraine; joverness.
Rare Cerebrovascular accident/stroke; exacerbation of epilepsy.
Very rare Exacerbation of chorea.

Musculoskeletal, connective tissue and bone disorders
Common Arthralgias; leg cramps.

Psychiatric disorders
Uncommon Changes in libido; mood disturbances; depression; delusions.
Rare Irritability.

Vascular disorders
Uncommon Venous thrombosis; pulmonary embolism.
Rare Superficial thrombophlebitis.

General disorders and administration site conditions
Uncommon Pruritus.

Skin and subcutaneous tissue disorders
Common Alopecia.
Uncommon Chloasma/melasma; hirsutism; pruritus; tinea.
Rare Erythema multiforme; erythematous nodules.

Hepato-biliary disorders
Uncommon Gallbladder disease.
Rare Cholestatic jaundice.

Immune system disorders
Uncommon Hypersensitivity.
Rare Urticaria; angioedema; anaphylactic/anaphylactoid reactions.

Metabolism and nutrition disorders
Rare Glucose intolerance.
Very rare Exacerbation of porphyria; hypocalcemia (in patients with disease that can predispose to severe hypocalcemia).

Eye disorders
Uncommon Intolerance to contact lenses.
Rare Retinal vascular thrombosis.

Cardiac disorders
Rare Myocardial infarction.

Respiratory, thoracic and mediastinal disorders
Rare Exacerbation of asthma manifestations.

Investigations
Common Changes in weight (increase or decrease) increased triglycerides.
Very rare Increased in blood pressure.

OVERDOSAGE
Symptoms of overdosage of estrogen-containing products in adults and children may include nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue; withdrawal bleeding may occur in females. There is no specific antidote and further treatment if necessary should be symptomatic.

MODE OF ACTION
Estrogens generally act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue. Circulating estrogens modulate the partial illumination of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), through a negative feedback mechanism. The estrogen overexpression may reduce the levels of these gonadotropins seen in postmenopausal women.

PHARMACODYNAMICS, CLINICAL EFFICACY
Effects on vasomotor symptoms
In the first year of the Health and Osteoporosis, Progestin and Estrogen (HOPE) Study, a total of 2,925 postmenopausal women (average age 53.3 ± 4.9 years) were randomly assigned to one of eight treatment groups, receiving either placebo or conjugated estrogens, with or without medroxyprogesterone acetate. Efficacy for vasomotor symptoms was assessed during the first 12 weeks of treatment in a subset of symptomatic women (n = 2411) who had at least seven moderate-to-severe hot flushes daily, or at least 50 moderate-to-severe hot flushes during the week before randomization. With CE (0.3mg, 0.45mg, and 0.625mg tablets), the relief of both the frequency and severity of moderate-to-severe vasomotor symptoms was shown to be statistically improved compared with placebo at weeks 4 and 12.

Table below shows the adjusted mean number of hot flushes in the CE 0.3mg, 0.45mg, and 0.625mg and placebo treatment groups over the initial 12-week period.

<table>
<thead>
<tr>
<th>Region Evaluated</th>
<th>Treatment Group</th>
<th>No. of Subjects</th>
<th>Change from Baseline (%) Adjusted Mean ± SE</th>
<th>P-Value vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>L2 to L4 BMD</td>
<td>0.625</td>
<td>83</td>
<td>1.17 ± 0.15</td>
<td>2.45 ± 0.37</td>
</tr>
<tr>
<td>Total BMD</td>
<td>0.625</td>
<td>84</td>
<td>1.15 ± 0.06</td>
<td>0.68 ± 0.17</td>
</tr>
<tr>
<td>Femoral Neck BMD</td>
<td>0.625</td>
<td>85</td>
<td>0.91 ± 0.14</td>
<td>1.82 ± 0.45</td>
</tr>
<tr>
<td>Femoral Trochanter BMD</td>
<td>0.625</td>
<td>84</td>
<td>0.76 ± 0.12</td>
<td>3.62 ± 0.58</td>
</tr>
</tbody>
</table>
Effects on female hypogonadism

In clinical studies of delayed puberty due to female hypogonadism, breast development was induced by doses as low as 0.15mg. The dosage may be gradually titrated upward to 6 to 7.5mg per day or as needed to achieve appropriate bone age advancement and eventual epiphyseal closure. Available data suggest that chronic dosing with 0.625mg is sufficient to induce clinical cyclic menstrual with sequential progesterone treatment and to maintain bone mineral density after skeletal maturity is achieved.

Women's Health Initiative Studies (WHI)
The Women's Health Initiative (WHI) enrolled approximately 17,000 predominantly healthy, postmenopausal women in two substudies to assess the risks and benefits of conjugated estrogen (CE) [0.625 mg/day] alone or in combination with medroxyprogesterone acetate (MPA) [0.25mg/2.5 mg daily] compared to placebo. The primary endpoint was the incidence of coronary heart disease (CHD), i.e., non-fatal myocardial infarction (MI), silent MI and death. The primary safety endpoint was incidence of invasive breast cancer. The substudy did not evaluate the effect of hormone replacement therapy on menopausal symptoms.

The estrogen-alone substudy was stopped early because an increased risk of stroke was observed, and it was deemed that further information obtained regarding the risks and benefits of estrogen alone in predetermined primary endpoints.

No overall effect on coronary heart disease (CHD) events (defined as non-fatal MI, silent MI, or death, due to CHD) was noted compared to women receiving estrogen alone compared with placebo. Results of the estrogen-alone substudy, which included 10,727 women (age range of 65 to 79 years; 75.3% White, 15.1% Black, 6.1% Hispanic, 6.8% Other), after an average follow-up of 6.8 years, are presented in the table below.

In the estrogen-alone substudy of WHI, there was no significant overall effect on the relative risk (RR) of CHD (RR 0.95, 95% confidence interval [CI] 0.76-1.16), a slightly elevated RR of CHD was reported for the early follow-up period and diminished over time. There was no significant effect on the RR of invasive breast cancer (RR 0.80, 95% CI 0.62-1.04) or non-invasive breast cancer (RR 1.08, 95% CI 0.75-1.55). Reported estrogen use was associated with a statistically significant increased risk of stroke (RR 1.37, 95% CI 1.03-1.83) and deep vein thrombosis (DVT) (RR 1.47, 95% CI 1.06-2.06). The RR of PE (RR 1.37, 95% CI 0.90-2.07) was not significantly increased. A statistically significant reduced risk of hip, vertebral and total fractures was reported relative to estrogen use (RR 0.65, 95% CI 0.45-0.94), (RR 0.69, 95% CI 0.43-0.94), (RR 0.73, 95% CI 0.50-0.87), respectively. The estrogen-alone substudy did not report a statistically significant effect on death due to other causes (RR 1.08, 95% CI 0.88-1.33) or an effect on overall mortality risk.

### Table below describes the primary results of the Estrogen-alone substudy stratified by age at baseline.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Women's Health Initiative Estrogen-alone Substudy Results Stratified by Age at Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>AGE</strong></td>
</tr>
<tr>
<td></td>
<td>50-59 years</td>
</tr>
<tr>
<td><strong>Events</strong></td>
<td></td>
</tr>
<tr>
<td><strong>CHD events</strong></td>
<td>0.95 (0.78-1.16)</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>1.01 (0.71-1.43)</td>
</tr>
</tbody>
</table>

### RELATIVE AND ABSOLUTE RISK SIGNIFICANCE IN THE ESTROGEN-ALONE SUBSTUDY OF WHI

**Event** | Relative Risk | CE vs. Placebo | Placebo | CE | Absolute Risk per 10,000 Women
--- | --- | --- | --- | --- | ---
CHD events | 0.95 (0.78-1.16) | 57 | 54 | 57 | 54 | 57 | 54 |
Non-fatal MI | 0.91 (0.73-1.14) | 43 | 40 | 43 | 40 | 43 | 40 |
CHD death | 1.01 (0.71-1.43) | 16 | 11 | 16 | 11 | 16 | 11 |
All Stroke | 1.33 (1.05-1.68) | 33 | 45 | 33 | 45 | 33 | 45 |
Ischemic | 1.95 (1.19-2.15) | 25 | 36 | 25 | 36 | 25 | 36 |
Deep vein thrombosis | 1.47 (1.06-2.06) | 15 | 23 | 15 | 23 | 15 | 23 |
Pulmonary embolism | 1.37 (0.90-2.07) | 10 | 14 | 10 | 14 | 10 | 14 |
Invasive breast cancer | 0.60 (0.52-0.69) | 34 | 29 | 34 | 29 | 34 | 29 |
Colorectal cancer | 1.06 (0.75-1.55) | 16 | 17 | 16 | 17 | 16 | 17 |
Hip fracture | 0.65 (0.45-0.94) | 19 | 12 | 19 | 12 | 19 | 12 |
Vertebral fracture | 0.64 (0.44-0.93) | 18 | 11 | 18 | 11 | 18 | 11 |
Lower arm/verterbral fracture | 0.68 (0.47-0.72) | 59 | 35 | 59 | 35 | 59 | 35 |
Total fractures | 0.71 (0.54-0.86) | 197 | 149 | 197 | 149 | 197 | 149 |
Death due to other causes | 1.06 (0.88-1.32) | 50 | 53 | 50 | 53 | 50 | 53 |
Overall mortality | 1.04 (0.88-1.22) | 75 | 79 | 75 | 79 | 75 | 79 |
Global Index | 1.02 (0.92-1.13) | 201 | 206 | 201 | 206 | 201 | 206 |

a Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
b Results are based on capacitally adjudicated data for an average follow-up of 7.1 years.
c Not included in global index.
d Results are based on average follow-up of 6.8 years.
e All deaths, except those from breast or colorectal cancer, definite/probable CHD, PE or cerebrovascular disease.
f A subset of the events was combined in a "global index" dataset as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes.

### AVAILABILITY
Blister strips of 30's packed in a carton with direction circular.

### STORAGE AND SHELF LIFE
Protect from heat and moisture, and shelf life is 3 years.