For the use of a Gynecologist only

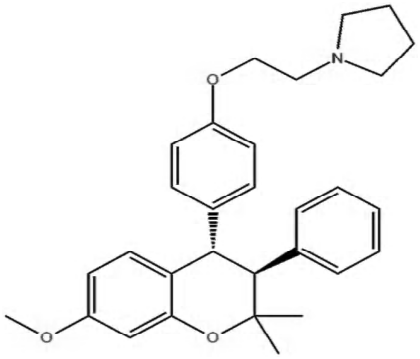
SEVISTA
Ormeloxifene 60mg Uncoated Tablet

COMPOSITION

Each uncoated tablet contains: Ormeloxifene hydrochloride I.P. 60mg

DESCRIPTION:

Sevista [INN: ormeloxifene; 3, 4 Trans - 2, 2 - dimethyl- 3- phenyl– 4- {p-(beta-pyrrolidinoethoxy) phenyl} -7-methoxychroman hydrochloride] is a nonsteroidal selective estrogen receptor modulator with anti-oestrogenic actions and weak oestrogenic activity. Ormeloxifene has the molecular formula C_{30}-H_{35}-N-O_3 and a molecular weight of 457.6 with the following structural formula:



CLINICAL PHARMACOLOGY:

Mechanism of Action:

Ormeloxifene is a selective estrogen receptor modulator that exerts antiestrogenic effects. Such anti-estrogens are expected to exert contraceptive effects and normalize the bleeding from uterine cavity by regularizing the expression of uterine endometrial estrogen receptors. This has been proposed to be the mechanisms of action of ormeloxifene in Dysfunctional Uterine Bleeding. Ormeloxifene exerts potent antiestrogen but also has weak estrogenic and antiprogestational actions.

Ormeloxifene inhibits implantation via inhibition of endometrial receptivity to blastocyst signals by antagonism of action of nidatory estrogen, without altering the concentration or secretion pattern of nidatory estrogen and progesterone, hypothalamo-pituitary-ovarian axis, follicle maturation, ovulation, mating behavior, gamete transport or fertilization, and preimplantation development of embryos. Ormeloxifene suppresses the receptors in the reproductive organs like the ovaries, uterus and breasts. But it stimulates the estrogen receptors of other organs like the bones. Ormeloxifene, in addition to its competitive antagonism at the estrogen receptor level, promotes the conversion of intracellular estradiol (E2) to estrone (E1), a biologically less active form, by activating 17-β-hydroxysteroid dehydrogenase II, thus decreasing the estrogen receptor

pool. Moreover ormeloxifene causes anti-progestational effects in the uterus by virtue of its anti-oestrogenic profile rather than by blocking the progesterone receptors.

An *in-vitro* competitive receptor interaction study has shown that ormeloxifene competes with radio labeled estradiol (E2) for binding with cytosol receptors (derived from immature rat uterus). Administration of ormeloxifene (25mcg dose) to 21 day old female rats (CF strain) was found to cause a slow build up of the nuclear receptor levels and their prolonged retention upto 72 hrs, while the cytosol receptor replenishment occurred much faster in estradiol treated animals. It not only blocks cytosol receptor but also causes their prolonged depletion and therefore its action lasts long after the drug has been withdrawn, unlike any other drug in use so far. Ormeloxifene activity in a series of *in vivo* and *in vitro* biological assays is reflective of the Selective Estrogen Receptor Modulator (SERM) profile. Their ability to (1) bind to the estrogen receptor, (2) antagonize estrogen-stimulated proliferation of MCF-7 cells *in vitro*, (3) stimulate TGF-beta 3 gene expression in cell culture, (4) inhibit the uterine effects of ethynyl estradiol in immature rats, and (5) potently reduce serum cholesterol and protect against osteopenia in ovarectomised (OVX) rats without estrogen – like stimulation of uterine tissue.

Pharmacokinetic

Absorption

Following a single 60-mg oral dose, Ormeloxifene is rapidly absorbed, with a maximum serum concentration (Cmax) varying from 117 to 129 ng/ml, and was observed 4 h after drug ingestion. However, in healthy subjects who received 30 mg ormeloxifene as oral tablets, it was shown that Cmax was 30.45 to 78.41 ng/ml after 3 to 8 h. The serum concentration–time curve ($AUC_{0-\infty}$) averaged to 5199±1388 ng h/ml.

Multiple oral dosing of ormeloxifene (30 mg twice a week for 12 weeks) in three women, Cmax varied from 40.91 to 69.29 ng/mL and occurred 6 to 8 h after the first 30-mg dose and was similar to that observed in normal females after a single 30-mg oral dose. Repeated administration did not cause any significant difference in Cmax, tmax, $AUC\tau$ or Css between the first and 24th dose, indicating insignificant accumulation during multiple dosing. Ninety-five percent steady-state concentrations were reached after 3.98–6.3 doses of ormeloxifene.

Distribution

Ormeloxifene is widely distributed within the body due to its high lipid solubility. In healthy

women, the apparent volume of distribution (Vd/F) was higher than the total body fluid and the mean residence time (MRT) was 128 days. Moreover, nursing females showed comparable Vd/F to that of non nursing females treated orally. Ormeloxifene binds strongly to serum albumin in healthy subjects (≥90%) in the individual serum samples with intersubject variability in protein binding of ormeloxifene. The binding increases with an increase in total protein content. It exhibits low-affinity, high-capacity binding with plasma albumin in human with a Kd value of 13.19×10^{-6} M. It does not compete with cortisol, estradiol, progesterone, testosterone, dihydrotestosterone or nonsteroidal estrogen agonist diethylstilbestrol or antagonists tamoxifen and nafoxidene, and is unlikely to displace steroids from specific steroid-binding plasma proteins, but in target tissues, e.g., the endometrium, it competes with estradiol for binding to estrogen receptor and shows an antiestrogenic activity.

Metabolism and Excretion

Ormeloxifene is extensively metabolized by rat liver homogenate. The 2-^{12}C-ormeloxifene is metabolized by rat liver homogenate *in vitro* to biologically active (7-desmethyl chroman, 2-desmethyl chroman and 2-monomethyl chroman) and inactive metabolites, with active metabolites contributing to estrogen agonistic and anti-implantation activities, while inactive metabolites accounting for its gradual metabolic disposition. All the three biologically active metabolites constitute its demethylated products showing 100% anti-implantation activity at 0.25, 0.25 and 2 mg/kg oral doses, respectively. Of these, 7-desmethyl ormeloxifene has earlier been considered as the possible active metabolite of ormeloxifene *in vivo*. A marked increase in activity of hepatic microsomal aniline hydroxylase, aminopyrine N-demethylase, cytochrome P450 and cytochrome b_5, indicating rapid disposal of the compound from the body, has also been observed in adult female rhesus monkeys treated with 25 mg/kg dose of ormeloxifene 8 h before autopsy. No effect, however, has been observed on activity of any enzyme of hepatic microsomal mixed function oxygenase system at its single contraceptive (2.5 mg/kg) dose. Studies regarding the metabolism of ormeloxifene in humans are scarce. In serum and milk, the demethylated metabolite (7-desmethyl ormeloxifene) has been reported after the oral administration of ormeloxifene to healthy volunteers. Unchanged ormeloxifene recovered in rat feces accounted for ≥26% of the administered ormeloxifene dose, thus indicating extensive metabolism.

Systemic clearance (0.14±0.04 L/h per kilogram) was 1.5 times higher than renal plasma flow; sites other than the kidney appear to be implicated in clearing the ormeloxifene.

INDICATIONS

Ormeloxifene is recommended for the treatment of Dysfunctional Uterine Bleeding (DUB) in women of reproductive age groups.

CONTRAINDICATIONS

Ormeloxifene should not be administered to women suffering from jaundice or severe hepatic dysfunction or chronic cervicitis or cervical hyperplasia or chronic illnesses like tuberculosis, renal disease. It should not be administered to women with history of hypersensitivity to Ormeloxifene or excipient of the product.

WARNING

Deviation from the usage instruction may not give the best results. Bi-weekly and weekly schedules are to be continued irrespective of menstrual periods.

Ormeloxifene has contraceptive properties. Women taking Ormeloxifene for DUB may also experience contraceptive effect. In the event of women desiring the pregnancy Ormeloxifene has to be discontinued. It may take upto a period of 6 months for a woman to conceive after discontinuing Ormeloxifene. Women desiring contraception should adhere to the contraceptive schedule. For a period of first 2 months of use a barrier contraceptive must be used in addition to ormeloxifene.

PRECAUTION

Occasionally, the menstrual cycle is likely to be prolonged in some users; delayed menstruation is of no consequence if tablets have not been missed. However, if the delay exceeds 15 days, investigations should be carried out to rule out pregnancy.

In case of a conception while taking Ormeloxifene the treatment should be discontinued under the advice of treating physician.

DRUG-DRUG INTERATIONS

Pharmacokinetic interactions commonly occur via drug metabolizing enzymes or drug transporters. Study done in rat describes the influence of the co-administration of various commonly used drugs on the pharmacological and pharmacokinetic profiles of ormeloxifene at its contraceptive dose in rats. The results revealed that the pharmacological activity of ormeloxifene remained unaltered with the co-administration of ciprofloxacin, cefixime, metronidazole, amlodipine, atenolol, theophylline, metformin, pioglitazone and glibenclamide.

Co-administration of tetracycline yielded significantly higher Cmax (35%) and a shorter time to reach Cmax (tmax) for ormeloxifene (42%) than those obtained in the control group of females. Inclusion of lactic acid bacillus spores in the regimen resulted in similar effects with increase in Cmax (47%) and AUC0–∞ (34%) of ormeloxifene with a significant decrease in tmax. Other parameters such as half-life, apparent clearance, Vd/F and MRT of ormeloxifene were not affected by either of the treatment.

ADVERSE REACTIONS

In clinical studies conducted so far in women of reproductive age group, Ormeloxifene has been reported to be safe and free from typical side effects of steroidal oral contraceptives such as weight gain, fluid retention, hypertension, etc. The entire course of therapy was free of drug-induced vaginal discharge, spotting, breakthrough bleeding or menorrhagia. In clinical trial conducted in forty-two women with menorrhagia the reported adverse effects are ovarian cyst, cervical erosion and discharge, gastric dyspepsia, vague abdominal pain and headache. Because clinical trials are conducted under widely varying conditions, it is not always possible to reliably estimate adverse effects frequency or establish a causal relationship to drug exposure.

OVERDOSAGE

In the event of overdosage, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

DOSAGE SCHEDULE AND ADMINISTRATION

The drug should be administered orally in the form of tablet (60 mg) twice a week(on Sunday and Wednesday), for the first 12 weeks and then once a week for another 12 weeks(on Sunday or Wednesday).

Expiry date Do not use later than the date of expiry.

Storage Keep in a dry place at a temperature not exceeding 30°C

Presentation SEVISTA is available as strip of 8 tablets

MARKETED BY

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