

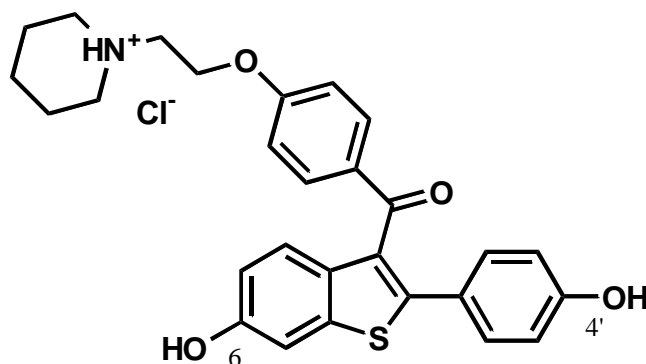
EVIFYNE

Raloxifene Hydrochloride

NAME OF THE MEDICINE

EVIFYNE (raloxifene hydrochloride)

The active ingredient in EVIFYNE tablets is raloxifene hydrochloride. Chemically, raloxifene hydrochloride is methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3-yl]-[4-[2-(1-piperidiny)ethoxy]phenyl]-, hydrochloride and its empirical formula is $C_{28}H_{27}NO_4S \cdot HCl$ which corresponds to a molecular weight of 510.05.



The CAS number for raloxifene HCl is 82640-04-8. The CAS number for raloxifene free base is 84449-90-1.

DESCRIPTION

Raloxifene hydrochloride is an off-white to pale-yellow solid that is very slightly soluble in water. Each film coated tablet contains 60 mg raloxifene hydrochloride, which is equivalent to 56 mg raloxifene free base. The tablets also contain povidone, polysorbate 80, lactose anhydrous, lactose, crospovidone, magnesium stearate, Color Mixture White YS-1-18027-A, Carnauba Wax, OPACODE BLUE 2-1-10537G and OPACODE S-1-10537G BLUE.

PHARMACOLOGY

Longterm post-menopausal health and the role of oestrogen

Oestrogen exerts agonistic effects on a number of bodily tissues. For example, oestrogen affects the structure and integrity of bone.

Decreases in oestrogen levels after oophorectomy or menopause lead to increases in bone resorption, accelerated bone loss and increased risk of fracture. Bone is initially lost rapidly because the compensatory increase in bone formation is inadequate to offset resorptive losses. This imbalance between resorption and formation is related to loss of oestrogen, and may also involve age-related impairment of osteoblasts or their precursors. Vertebral fractures are the most common type of osteoporotic fracture in post-menopausal women. These fractures are associated with substantial morbidity and impairment in quality of life.

Managing post-menopausal changes that are associated with decreased oestrogen is a challenge. Other conditions not related to decreased oestrogen levels, such as cancers of the breast and uterus, also increase post-menopause.

Mode of action

Raloxifene has agonistic effects at some oestrogen receptors, antagonistic effects at other oestrogen receptors and has been referred to as a selective oestrogen receptor modulator (SERM). It exerts the positive effects of oestrogen on bone and lipid metabolism, while specifically antagonising some of the potentially negative effects of oestrogen on uterine and breast tissues. The agonistic effect of raloxifene on bone and lipid metabolism has been shown to be dose dependent.

Raloxifene decreases resorption of bone and normalises bone turnover to the pre-menopausal range. These effects on bone are manifested as reductions in the serum and urine levels of bone turnover markers, decreases in bone resorption, increases in bone mineral density (BMD) and decreases in incidences of fractures.

The biological actions of raloxifene, like those of oestrogen, are mediated through binding to oestrogen receptors. This binding results in differential expression of multiple oestrogen-regulated genes in different tissues. Recent data suggest that the oestrogen receptor can regulate gene expression by at least two distinct pathways which are ligand-, tissue-, and/or gene-specific.

Pharmacokinetic properties

Absorption. Raloxifene is absorbed rapidly after oral administration. Although approximately 60% of an oral dose is absorbed, presystemic glucuronide conjugation is extensive and absolute bioavailability is 2.0%. The time to reach average maximum plasma concentration and bioavailability are functions of absorption, systemic interconversion and enterohepatic cycling of raloxifene and its glucuronide metabolites.

Distribution. Raloxifene is distributed extensively in the body. The volume of distribution is not dose dependent.

Protein Binding. Approximately 98% to 99% of raloxifene is bound *in vitro* to plasma proteins, including both albumin and α -1-acid glycoprotein. Raloxifene is not displaced *in vitro* by its glucuronide conjugates.

Metabolism. Raloxifene comprises less than 1% of the combined concentrations of raloxifene and the glucuronide metabolites in plasma. Raloxifene and its glucuronide conjugates are interconverted by reversible systemic metabolism and enterohepatic cycling, prolonging raloxifene's plasma elimination half-life to an average of 27.7 hours after oral dosing.

Results from single oral doses of raloxifene predict multiple dose pharmacokinetics, although increasing doses of raloxifene result in slightly less than a proportional increase in the area under the plasma concentration/time curve.

Excretion. The majority of a dose of raloxifene and its glucuronide metabolites are excreted within 5 days, primarily in the faeces, with less than 6% excreted in the urine.

Special Populations

Renal Insufficiency - Less than 6% of the total dose is eliminated in urine. In the osteoporosis treatment and prevention trials, blood levels of raloxifene and its metabolite were not affected by renal function in women having estimated creatinine clearance as low as 21 mL/min.

Hepatic Insufficiency - The pharmacokinetics of a single dose of raloxifene in patients with hepatic dysfunction have been compared to that in healthy individuals. Plasma raloxifene concentrations were approximately 2.5-fold higher than in controls and correlated with total bilirubin concentrations.

CLINICAL TRIALS

Clinical data indicate that raloxifene, a selective oestrogen receptor modulator (SERM), has oestrogen-like effects on bone (increase in BMD) and on lipid (decrease in total and LDL cholesterol levels) metabolism. Preclinical data in rodents suggest that raloxifene is an oestrogen antagonist in uterine and breast tissues. Clinical data demonstrate that raloxifene lacks oestrogen-like effects on uterus and breast tissue.

Skeletal effects

In post-menopausal women with osteoporosis, raloxifene reduces the risk of vertebral fractures. Raloxifene also increases BMD of the spine, hip and total body. Similarly, in post-menopausal women without osteoporosis, raloxifene preserves bone mass and significantly increases BMD of the hip and spine.

i) Treatment of osteoporosis. The effects of raloxifene on fracture incidence and BMD in post-menopausal women with osteoporosis were examined at 3 years in a large randomised placebo-controlled, double-blind osteoporosis treatment trial. The study population consisted of 7705 post-menopausal women with osteoporosis as defined by: a) low BMD (vertebral or hip BMD at least 2.5 standard deviations below the mean value for healthy young women) without baseline vertebral fractures, or b) one or more baseline vertebral fractures. Women enrolled in this study had a median age of 67 years (range 31 to 80) and a median time since menopause of 19 years. All women received calcium (500 mg/day) and vitamin D (400-600 IU/day).

Raloxifene hydrochloride, 60 mg administered once daily, increased spine and hip BMD by 2-3% and total body and ultradistal radius BMD by 1-2%, and decreased the incidence of one or more vertebral fractures by as much as 55% (Table 1) compared to an active therapy of calcium plus vitamin D supplemented placebo. Raloxifene reduced the incidence of vertebral fractures whether or not patients had experienced a previous fracture.

Table 1. Effect of Raloxifene Hydrochloride 60 mg on Risk of Vertebral Fractures

	Number of Patients		Relative Risk (95% CI)
	Raloxifene	Placebo	
Patients with no baseline fracture ^a	n=1401	n=1457	
Number of patients with ≥1 new vertebral fractures	27	62	0.45 (0.29, 0.71)
Patients with ≥1 baseline fractures ^a	n=858	n=835	
Number of patients with ≥1 new vertebral fractures	121	169	0.70 (0.56, 0.86)
All randomised patients	n=2557	n=2576	
Number of patients with ≥1 new clinical (painful) vertebral fracture	47	81	0.59 (0.41, 0.83)

^aIncludes all patients with baseline and at least one follow-up radiograph.

ii) Prevention of osteoporosis. The effects of raloxifene on BMD in post-menopausal women were examined in three large randomised, placebo-controlled, double-blind osteoporosis prevention trials: (1) a North American trial enrolled 544 women; (2) a European trial, 601 women; and (3) an international trial, 619 women who had undergone hysterectomy. In these trials, all women received calcium supplementation (400 to 600 mg/day). Women enrolled in these studies had a median age of 54 years and a median time since menopause of 5 years (less than 1 year up to 15 years post-menopause). The majority of the women were Caucasian (93.5%). Women were included if they had spine bone mineral density between 2.5 standard deviations below and 2 standard deviations above the mean value for healthy young women. The mean T scores (number of standard deviations above or below the mean in healthy young women) ranged from -1.01 to -0.74 for spine BMD and included women both with normal and low BMD.

Raloxifene produced significant increases in bone density of the hip (1.3% to 2.4%) and spine (1.8% to 2.4%) compared to placebo (Table 2). Raloxifene also increased BMD compared with placebo in the total body by 1.3% to 2.0% and in Ward's Triangle (hip) by 3.1% to 4.0%. The effects of raloxifene on forearm BMD were inconsistent between studies.

Table 2. Raloxifene hydrochloride (60 mg once daily) related increases in BMD for the three osteoporosis prevention studies expressed as mean percentage increase versus calcium-supplemented placebo at 24 months^a

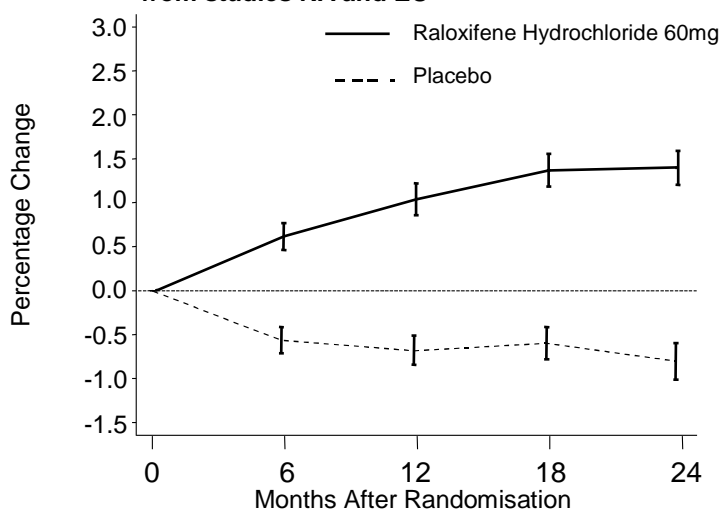
Site	Study		
	NA %	EU %	INT ^b %
Total Hip	2.0	2.4	1.3
Femoral Neck	2.1	2.5	1.6
Trochanter	2.2	2.7	1.3
Intertrochanter	2.3	2.4	1.3
Lumbar Spine	2.0	2.4	1.8

Abbreviations: NA = North America, EU = European, INT = International

^a Intent-to-treat analysis; last observation carried forward.

^b All women in the study had previously undergone hysterectomy.

Fig 1. Total hip mean percentage change from baseline – All placebo and raloxifene subjects 24-month-data from studies NA and EU^a



^a Intent to treat analysis, last observation carried forward.

iii) Calcium kinetics. Raloxifene and oestrogen affect bone remodelling and calcium metabolism similarly. In a 31-week open-label radiocalcium kinetics study, 33 early post-menopausal women were randomised to treatment with once-daily raloxifene hydrochloride 60 mg, cyclic oestrogen/progestin (HRT) or no treatment. Raloxifene was associated with reduced bone resorption and a mean positive shift in calcium balance of 60 mg per day, due primarily to decreased urinary calcium losses. These findings were similar to those observed with HRT.

iv) Histomorphometry (bone quality). In the osteoporosis treatment study, bone biopsies for qualitative and quantitative histomorphometry were obtained at baseline and after 2 years of treatment with placebo, raloxifene hydrochloride 60-mg or raloxifene hydrochloride 120-mg daily. There were 56 paired biopsies evaluable (24 placebo, 20 raloxifene hydrochloride 60-mg and 12 raloxifene hydrochloride 120-mg). Similarly to placebo-treated patients, in raloxifene-treated patients, normal bone quality was maintained;

specifically, there was no evidence of osteomalacia, marrow fibrosis, cellular toxicity or woven bone after 2 years of treatment.

The effects of EVIFYNE on bone histomorphometry were determined by pre-and post-treatment biopsies in a 6-month study of Caucasian post-menopausal women who received once-daily doses of EVIFYNE 60 mg or 0.625 mg conjugated oestrogens. Ten raloxifene-treated and 8 oestrogen-treated women had evaluable bone biopsies at baseline and after 6 months of therapy. Bone in EVIFYNE-treated and oestrogen-treated women showed no evidence of mineralisation defects, woven bone or marrow fibrosis.

Effects on the endometrium

In clinical trials, raloxifene did not stimulate the post-menopausal uterine endometrium. Compared to placebo, raloxifene was not associated with spotting or bleeding or endometrial hyperplasia. Nearly 3,000 transvaginal ultrasound (TVUs) examinations were evaluated from 831 women in all dose groups. Raloxifene treated women consistently had an endometrial thickness which was indistinguishable from placebo. Furthermore, there were no differences between the raloxifene and placebo groups with respect to the incidence of reported uterine bleeding.

Endometrial biopsies taken after six months of therapy with raloxifene demonstrated nonproliferative endometrium in all patients. In addition, in a study with 2.5 times the recommended daily dose of raloxifene there was no evidence of endometrial proliferation and no increase in uterine volume.

In the osteoporosis treatment trial, endometrial thickness was evaluated annually in a subset of the study population (1781 patients) for three years. Placebo-treated women had a 0.27 mm mean decrease from baseline in endometrial thickness over 3 years, whereas the raloxifene hydrochloride 60-mg-treated women had a 0.06 mm mean increase (not different from baseline).

After three years, raloxifene did not increase the risk of endometrial or ovarian cancer.

Effects on breast tissue

Preclinical data in rodents suggest that raloxifene is an oestrogen antagonist in uterine and breast tissues. Across all placebo-controlled trials, raloxifene was indistinguishable from placebo with regard to frequency and severity of breast symptoms. Raloxifene was associated with significantly fewer breast symptoms (swelling, tenderness, breast pain) than reported by patients receiving oestrogens, with or without added progestins.

MORE Trial

The effect of EVIFYNE on the incidence of breast cancer was assessed as a secondary safety endpoint in a randomised, placebo-controlled, double-blind, multinational osteoporosis treatment trial in postmenopausal women. After 4 years, EVIFYNE, 60 mg administered once daily, reduced the incidence of all breast cancers by 62%, compared with placebo (HR 0.38, 95% CI 0.22-0.67). EVIFYNE reduced the incidence of invasive breast cancer by 71%, compared with placebo (adjusted relative risk (ARR) 3.1 per 1000 women-years); this was primarily due to an 80% reduction in the incidence of ER-positive invasive breast cancer in the EVIFYNE group compared with placebo. Table 3 presents efficacy and selected safety outcomes.

CORE Trial

The effect of EVIFYNE on the incidence of invasive breast cancer was evaluated for 4 additional years in a follow-up study conducted in a subset of postmenopausal women originally enrolled in the MORE osteoporosis treatment trial. Women were not re-randomised; the treatment assignment from the osteoporosis treatment trial was carried forward to this study. EVIFYNE, 60 mg administered once daily, reduced the incidence of invasive breast cancer by 56%, compared with placebo (ARR 3.0 per 1000 women-years); this was primarily due to a 63% reduction in the incidence of ER-positive invasive breast cancer in the EVIFYNE group compared with placebo. There was no reduction in the incidence of ER-negative breast cancer. In the osteoporosis treatment trial and the follow-up study, there was no difference in incidence of noninvasive breast cancer between the EVIFYNE and placebo groups. Table 3 presents efficacy and selected safety outcomes.

MORE-CORE Combined

In a subset of postmenopausal women followed for up to 8 years from randomisation in MORE to the end of CORE, EVIFYNE, 60 mg administered once daily, reduced the incidence of invasive breast cancer by 60% in women assigned EVIFYNE (n=1355) compared with placebo (n=1286) (HR 0.40, 95% CI 0.21, 0.77; ARR 1.95 per 1000 women-years); this was primarily due to a 65% reduction in the incidence of ER-positive invasive breast cancer in the EVIFYNE group compared with placebo.

Table 3: EVIFYNE (60 mg Once Daily) vs. Placebo on Outcomes in Postmenopausal Women with Osteoporosis

Outcomes	MORE					CORE ^a				
	Placebo (n=2576)		EVIFYNE (n=2557)		HR (95% CI) ^b	Placebo (n=1286)		EVIFYNE (n=2725)		HR (95% CI) ^b
	n	IR ^b	n	IR ^b		n	IR ^b	n	IR ^b	
Invasive ^c breast cancer	38	4.36	11	1.26	0.29 (0.15, 0.56) ^d	20	5.41	19	2.43	0.44 (0.24, 0.83) ^d
ER ^{b,c} positive	29	3.33	6	0.69	0.20 (0.08, 0.49)	15	4.05	12	1.54	0.37 (0.17, 0.79)
ER ^{b,c} negative	4	0.46	5	0.57	1.23 (0.33, 4.60)	3	0.81	6	0.77	0.95 (0.24, 3.79)
ER ^{b,c} Unknown	5	0.57	0	0.00	N/A ^b	2	0.54	1	0.13	N/A ^b
Noninvasive ^{c,e} breast cancer	5	0.57	3	0.34	0.59 (0.14, 2.47)	2	0.54	5	0.64	1.18 (0.23, 6.07)
Clinical vertebral fractures	107	12.27	62	7.08	0.57 (0.42, 0.78)	N/A ^b	N/A ^b	N/A ^b	N/A ^b	N/A ^b
Death	36	4.13	23	2.63	0.63 (0.38, 1.07)	29	7.76	47	5.99	0.77 (0.49, 1.23)
Death due to stroke	6	0.69	3	0.34	0.49 (0.12, 1.98)	1	0.27	6	0.76	2.87 (0.35, 23.80)
Stroke	56	6.42	43	4.91	0.76 (0.51, 1.14)	14	3.75	49	6.24	1.67 (0.92, 3.03)
Deep vein thrombosis	8	0.92	20	2.28	2.50 (1.10, 5.68)	4	1.07	17	2.17	2.03 (0.68, 6.03)
Pulmonary Embolism	4	0.46	11	1.26	2.76 (0.88, 8.67)	0	0.00	9	1.15	N/A ^b
Endometrial and uterine cancer ^f	5	0.74	5	0.74	1.01 (0.29, 3.49)	3	1.02	4	0.65	0.64 (0.14, 2.85)
Ovarian cancer	6	0.69	3	0.34	0.49	2	0.54	2	0.25	0.47

					(0.12, 1.95)					(0.07, 3.36)
Hot flushes	151	17.31	237	27.06	1.61 (1.31, 1.97)	11	2.94	26	3.31	1.12 (0.55, 2.27)
Peripheral oedema	134	15.36	164	18.73	1.23 (0.98, 1.54)	30	8.03	61	7.77	0.96 (0.62, 1.49)
Cholelithiasis	45	5.16	53	6.05	1.18 (0.79, 1.75)	12	3.21	35	4.46	1.39 (0.72, 2.67)

^a CORE was a follow-up study conducted in a subset of 4011 postmenopausal women who originally enrolled in MORE. Women were not re-randomised; the treatment assignment from MORE was carried forward to this study. At CORE enrollment, the EVIFYNE group included 2725 total patients with 1355 patients who were originally assigned to raloxifene 60 mg once daily and 1370 patients who were originally assigned to raloxifene 120 mg at MORE randomisation.

^b Abbreviations: CI = confidence interval; ER = estrogen receptor; HR = hazard ratio; IR = annual incidence rate per 1000 women; N/A = not applicable.

^c Included 1274 patients in placebo and 2716 patients in EVIFYNE who were not diagnosed with breast cancer prior to CORE enrollment.

^d $p < 0.05$, obtained from the log-rank test, and not adjusted for multiple comparisons in MORE.

^e All cases were ductal carcinoma in situ.

^f Only patients with an intact uterus were included (MORE: placebo = 1999, EVIFYNE = 1950; CORE: placebo = 1008, EVIFYNE = 2138).

RUTH Trial

The effect of EVIFYNE on the incidence of invasive breast cancer was assessed in a randomised, placebo-controlled, double-blind, multinational study in 10,101 postmenopausal women at increased risk of coronary events. Women in this study had a median age of 67.6 years (range 55–92) and were followed for a median of 5.6 years (range 0.01–7.1). Eighty-four percent were Caucasian, 9.8% of women reported a first-degree relative with a history of breast cancer, and 41.4% of the women had a 5-year predicted risk of invasive breast cancer >1.66%, based on the modified Gail model.

EVIFYNE, 60 mg administered once daily, reduced the incidence of invasive breast cancer by 44% compared with placebo [absolute risk reduction (ARR) 1.2 per 1000 women-years]; this was primarily due to a 55% reduction in estrogen receptor (ER)-positive invasive breast cancer in the EVIFYNE group compared with placebo (ARR 1.2 per 1000 women-years). There was no reduction in ER-negative invasive breast cancer. Table 4 presents efficacy and selected safety outcomes.

Table 4: EVIFYNE (60 mg Once Daily) vs. Placebo on Outcomes in Postmenopausal Women at Increased Risk for Major Coronary Events

Outcomes	Placebo ^a (n=5057)		EVIFYNE ^a (n=5044)		HR (95% CI) ^b
	n	IR ^b	n	IR ^b	
Invasive breast cancer	70	2.66	40	1.50	0.56 (0.38, 0.83) ^c
ER ^b positive	55	2.09	25	0.94	0.45 (0.28, 0.72)
ER ^b negative	9	0.34	13	0.49	1.44 (0.61, 3.36)
ER ^b unknown	6	0.23	2	0.07	0.33 (0.07, 1.63)
Noninvasive ^d breast cancer	5	0.19	11	0.41	2.17 (0.75, 6.24)
Clinical vertebral fractures	97	3.70	64	2.40	0.65 (0.47, 0.89)
Death	595	22.45	554	20.68	0.92 (0.82, 1.03)
Death due to stroke	39	1.47	59	2.20	1.49 (1.00, 2.24)
Stroke	224	8.60	249	9.46	1.10 (0.92, 1.32)
Deep vein thrombosis	47	1.78	65	2.44	1.37 (0.94, 1.99)
Pulmonary embolism	24	0.91	36	1.35	1.49 (0.89, 2.49)
Endometrial and uterine cancer ^e	17	0.83	21	1.01	1.21 (0.64 - 2.30)
Ovarian cancer ^f	10	0.41	17	0.70	1.69 (0.78, 3.70)
Hot flushes	241	9.09	397	14.82	1.68 (1.43, 1.97)
Peripheral oedema	83	22.00	706	26.36	1.22 (1.09, 1.36)
Cholelithiasis ^g	131	6.20	168	7.83	1.26 (1.01, 1.59)

^a Note: There were a total of 76 breast cancer cases in the placebo group and 52 in the EVIFYNE group. For two cases, one in each treatment group, invasive status was unknown.

^b Abbreviations: CI = confidence interval; ER = estrogen receptor; HR = hazard ratio; IR = annual incidence rate per 1000 women.

^c p<0.05, obtained from the log-rank test, after adjusting for the co-primary endpoint of major coronary events.

^d All cases were ductal carcinoma in situ.

^e Only patients with an intact uterus were included (placebo = 3882, EVIFYNE = 3900).

^f Only patients with at least one ovary were included (placebo = 4606, EVIFYNE = 4559).

^g Only patients with an intact gallbladder at baseline were included (placebo = 4111, EVIFYNE = 4144).

The effect of EVIFYNE in reducing the incidence of invasive breast cancer was consistent among women above or below age 65 or with a 5-year predicted invasive breast cancer risk, based on the modified Gail model, <1.66%, or >1.66%. (The modified Gail model is described in the INDICATIONS section)

STAR Trial

The effects of EVIFYNE 60 mg/day versus tamoxifen 20 mg/day over 5 years on reducing the incidence of invasive breast cancer were assessed in 19,747 postmenopausal women in a randomised, double-blind trial conducted in North America by the National Surgical Adjuvant Breast and Bowel Project and sponsored by the National Cancer Institute. Women in this study had a mean age of 58.5 years (range 35–83), a mean 5-year predicted invasive breast cancer risk of 4.03% (range 1.66–23.61%), and 9.1% had a history of lobular carcinoma in situ (LCIS). More than 93% of participants were Caucasian. As of 31 December 2005, the median time of follow-up was 4.3 years (range 0.07–6.50 years).

EVIFYNE was not superior to tamoxifen in reducing the incidence of invasive breast cancer. The observed incidence rates of invasive breast cancer were EVIFYNE 4.4 and tamoxifen 4.3 per 1000 women per year. The effect of each treatment on invasive breast cancer was consistent when women were compared by baseline age, history of LCIS, history of atypical hyperplasia, 5-year predicted risk of breast cancer by the modified Gail model, or the number of relatives with a history of breast cancer. Fewer noninvasive breast cancers occurred in the tamoxifen group compared to the EVIFYNE group. Table 5 presents efficacy and selected safety outcomes.

Table 5: EVIFYNE (60 mg Once Daily) vs. Tamoxifen (20 mg Once Daily) on Outcomes in Postmenopausal Women at Increased Risk for Invasive Breast Cancer

Outcomes	EVIFYNE (n=9751)		Tamoxifen (n=9736)		RR (95% CI) ^a
	n	IR ^a	n	IR ^a	
Invasive breast cancer	173	4.40	168	4.30	1.02 (0.82, 1.27)
ER _a positive	115	2.93	120	3.07	0.95 (0.73, 1.24)
ER _a negative	52	1.32	46	1.18	1.12 (0.74, 1.71)
ER _a unknown	6	0.15	2	0.05	2.98 (0.53, 30.21)
Noninvasive breast cancer ^b	83	2.12	60	1.54	1.38 (0.98, 1.95)
DCIS ^a	47	1.20	32	0.82	1.46 (0.91, 2.37)
LCIS ^a	29	0.74	23	0.59	1.26 (0.70, 2.27)
Uterine cancer ^c	23	1.21	37	1.99	0.61 (0.34, 1.05)
Endometrial hyperplasia ^c	17	0.90	100	5.42	0.17 (0.09, 0.28)
Hysterectomy ^c	92	4.84	246	13.25	0.37 (0.28, 0.47)
Ovarian cancer ^d	18	0.66	14	0.52	1.27 (0.60, 2.76)
Ischemic heart disease ^e	138	3.50	125	3.19	1.10 (0.86, 1.41)
Stroke	54	1.36	56	1.42	0.96 (0.65, 1.42)
Deep vein thrombosis	67	1.69	92	2.35	0.72 (0.52, 1.00)
Pulmonary embolism	38	0.96	58	1.47	0.65 (0.42, 1.00)
Clinical vertebral	58	1.46	58	1.47	0.99 (0.68, 1.46)

fractures					
Cataracts ^f	43	10.34	435	13.19	0.78 (0.68, 0.91)
Cataract surgery ^f	240	7.17	295	8.85	0.81 (0.68, 0.96)
Death	104	2.62	109	2.76	0.95 (0.72, 1.25)
Oedema ^g	741	18.66	664	16.83	1.11 (1.00, 1.23)
Hot flushes	6748	169.91	7170	181.71	0.94 (0.90, 0.97)

^a Abbreviations: CI = confidence interval; DCIS = ductal carcinoma in situ; ER = estrogen receptor; IR = annual incidence rate per 1000 women; LCIS = lobular carcinoma in situ; RR = risk ratio for women in the EVIFYNE group compared with those in the tamoxifen group.

^b Of the 60 noninvasive breast cases in the tamoxifen group, 5 were mixed types. Of the 83 noninvasive breast cancers in the raloxifene group, 7 were mixed types.

^c Only patients with an intact uterus at baseline were included (tamoxifen = 4739, EVIFYNE = 4715).

^d Only patients with at least one intact ovary at baseline were included (tamoxifen = 6813, EVIFYNE = 6787).

^e Defined as myocardial infarction, severe angina, or acute ischemic syndromes.

^f Only patients who were free of cataracts at baseline were included (tamoxifen = 8342; EVIFYNE = 8333).

^g Peripheral oedema events are included in the term oedema.

INDICATIONS

EVIFYNE is indicated for the prevention and treatment of osteoporosis in post-menopausal women.

EVIFYNE is indicated for the reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis.

EVIFYNE is indicated for the reduction in the risk of invasive breast cancer in postmenopausal women at high risk of invasive breast cancer.

High risk of breast cancer is defined as at least one breast biopsy showing lobular carcinoma in situ (LCIS) or atypical hyperplasia, one or more first-degree relatives with breast cancer, or a 5-year predicted risk of breast cancer >1.66% (based on the modified Gail model). Among the factors included in the modified Gail model are the following: current age, number of first-degree relatives with breast cancer, number of breast biopsies, age at menarche, nulliparity or age of first live birth. Currently, no single clinical finding or test result can quantify risk of breast cancer with certainty.

CONTRAINDICATIONS

EVIFYNE is contraindicated in women who are or may become pregnant. Raloxifene may cause foetal harm when administered to a pregnant woman.

EVIFYNE is not indicated for premenopausal women. Safety of raloxifene in premenopausal women has not been established and its use is not recommended.

EVIFYNE is contraindicated in women with active or a past history of venous thromboembolic events (VTE), including deep vein thrombosis, pulmonary embolism and retinal vein thrombosis.

EVIFYNE is also contraindicated in women with hypersensitivity to raloxifene or other ingredients in the tablet.

EVIFYNE is contraindicated for use in males. It is only for use in post-menopausal women.

PRECAUTIONS

1. In a multi-centre double-blind, placebo-controlled, randomised, parallel study of 10,101 postmenopausal women with documented coronary heart disease or at increased risk for coronary events followed for a median of 5.6 years, there was an increased risk of mortality due to stroke in the group taking raloxifene, although the incidence of stroke, myocardial infarction, hospitalised acute coronary syndrome, cardiovascular mortality, or overall mortality was comparable to placebo. The incidence of stroke mortality was 1.5 per 1000 women per year for placebo versus 2.2 per 1000 women per year for raloxifene. The risk-benefit balance of raloxifene for treatment or prevention of osteoporosis, or reduction in risk of invasive breast cancer, in postmenopausal women with a history of stroke or other significant stroke risk factors, such as transient ischaemic attack or atrial fibrillation, should be considered when prescribing EVIFYNE.
2. Raloxifene is associated with an increased risk for venous thromboembolic events that appears to be similar to the reported risk associated with current use of hormone replacement therapy. The risk-benefit balance should be considered in patients at risk of VTEs (venous thromboembolic events) of any aetiology. Raloxifene should be discontinued in the event of a condition or illness leading to a prolonged period of immobilisation. Discontinuation should happen as soon as possible with illness, or from three days before prolonged immobilisation is likely. Therapy should not be restarted until the initiating condition has resolved and the patient is fully mobile. In addition, women taking raloxifene should be advised to move about periodically during prolonged travel.
3. Raloxifene is not effective in reducing vasodilatation (hot flushes) associated with oestrogen deficiency.
4. Raloxifene is metabolised primarily in the liver. Single doses of raloxifene given to patients with cirrhosis produced plasma concentrations of raloxifene which were approximately 2.5 times the controls. The increase correlated with total bilirubin concentrations. Until safety and efficacy have been evaluated further in patients with hepatic insufficiency, the use of raloxifene is not recommended in this patient population.
5. The concurrent use of raloxifene and systemic oestrogen for hormone replacement therapy (HRT) has not been studied systematically. Therefore, raloxifene should not be used concomitantly with systemic oestrogens.
6. Raloxifene has not been associated with endometrial proliferation (see CLINICAL TRIALS, Effects on the endometrium). Unexplained uterine bleeding should be considered abnormal and investigated as clinically indicated.

7. In patients with a history of oral oestrogen-induced hypertriglyceridaemia (>5.6 mmol/L), raloxifene may be associated with a marked increase in serum triglycerides. Patients with this medical history should have serum triglycerides monitored when taking raloxifene.
8. Raloxifene has no known effect on driving or the ability to use machinery.
9. EVIFYNE does not eliminate the risk of breast cancer. Patients should have breast examinations and mammograms before starting EVIFYNE and should continue regular breast examinations and mammograms in keeping with good medical practice after beginning treatment with EVIFYNE.

There are no data available regarding the effect of EVIFYNE on invasive breast cancer incidence in women with inherited mutations (BRCA1, BRCA2) to be able to make specific recommendations on the effectiveness of EVIFYNE. EVIFYNE is not indicated for the treatment of invasive breast cancer or reduction of the risk of recurrence. It has not been studied adequately in women with a prior history of breast cancer. It is not indicated for the reduction in risk of non-invasive breast cancer.

Effects on Fertility

Reproductive effects observed in animal studies are consistent with the known pharmacological profile of raloxifene. Oestrous cycling was disrupted in mice given dietary doses ≥ 15 mg/kg/day, and in rats at oral gavage doses ≥ 1 mg/kg/day, with a no-effect dose level of 0.1 mg/kg/day in the latter study. Fertility of female rats was abolished at dietary doses ≥ 5 mg/kg/day (no-effect dose not established). In one study, fertility of female rats dosed by oral gavage at 10 mg/kg/day was almost completely restored immediately after cessation of treatment and was completely restored after a 2-week recovery period. However, disruption of oestrous cycling and infertility persisted up to 5 weeks in a few rats dosed at 6-63 mg/kg/day in a dietary study. In rats becoming pregnant immediately after cessation of treatment at 10 mg/kg/day by oral gavage, litter size was reduced, gestation length was slightly increased and the timing of events in neonatal development was slightly altered; similar effects were not seen in animals mated after a 2-week recovery period. When given by oral gavage to mated female rats during the preimplantation period at 0.1 to 10 mg/kg/day, raloxifene delayed and disrupted embryo implantation resulting in prolonged gestation, and reduced litter size. Development of offspring to weaning was not affected. The reproductive effects of raloxifene in animal studies reflect the pharmacological activity of the drug and similar effects may occur if raloxifene is administered to pre-menopausal women.

Raloxifene is a potent antioestrogen in the rat uterus and prevented growth of oestrogen-dependent mammary tumours in rats and mice.

Use in Pregnancy - Pregnancy Category X

Raloxifene is only for use in post-menopausal women.

Raloxifene must not be taken by women of child bearing potential. Animal studies showed that raloxifene caused foetal malformations in rabbits and abnormalities in the reproductive system and impaired reproductive function in the female offspring of rats. These developmental effects were observed at pharmacologically active dose levels and similar effects on foetal development may occur if raloxifene is administered to a pregnant woman. If this drug is used mistakenly during pregnancy or the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to the foetus.

Use in Lactation

It is not known whether raloxifene is excreted in human or animal milk. In animal studies, oral administration of raloxifene (0.1 to 10 mg/kg/day) during pregnancy and lactation caused suppression of pup growth during lactation and histopathological changes in the reproductive system of female offspring; fertility of female offspring was impaired at the high dose level. Raloxifene's use, therefore, cannot be recommended in lactating women, as it may affect the development of the baby.

Carcinogenicity

In a 2-year carcinogenicity study in rats, an increase in ovarian tumours of granulosa/theca cell origin was observed in females given a dietary dose of 279 mg/kg/day (approximately 400 times the AUC in humans). In a 21-month dietary study in mice, there was an increased incidence of testicular interstitial cell tumours and prostatic adenomas and adenocarcinomas in males given 41 to 210 mg/kg/day (comparable to 4.7 to 24 times the AUC in humans) and prostatic leiomyoblastoma in males given 210 mg/kg/day. An increased incidence of ovarian tumours in female mice given dietary doses of 9 to 242 mg/kg/day (comparable to 0.3 to 34 times the AUC in humans) included benign and malignant tumours of granulosa/theca cell origin and benign tumours of epithelial cell origin. The female rodents in these studies were treated during their reproductive lives, when their ovaries were functional and highly responsive to hormonal stimulation.

Genotoxicity

Raloxifene was not genotoxic in assays of gene mutation, chromosomal damage, DNA damage or sister chromatid exchange.

INTERACTIONS WITH OTHER MEDICINES

Cholestyramine - Raloxifene should not be co-administered with cholestyramine or other anion exchange resins. The absorption and enterohepatic cycling of raloxifene is significantly reduced by cholestyramine.

Ampicillin and other oral antimicrobials - Peak concentrations of raloxifene are reduced by co-administration with ampicillin. This reduction is consistent with decreased enterohepatic cycling associated with antibiotic reduction of enteric bacteria. However, as the overall extent of absorption and the elimination rate of raloxifene are not affected, raloxifene can be concurrently administered with ampicillin. In the osteoporosis treatment trial, co-administered oral antimicrobial agents (including amoxicillin, cephalexin, ciprofloxacin, macrolide antibiotics, sulfamethoxazole/trimethoprim and tetracycline) had no effect on plasma raloxifene concentration.

Corticosteroids – The chronic administration of raloxifene in post-menopausal women has no effect on the pharmacokinetics of methylprednisolone given as a single oral dose.

Digoxin - Raloxifene has no effect on the pharmacokinetics of digoxin. In the osteoporosis treatment trial, co-administered digoxin had no effect on plasma raloxifene concentration.

Gastrointestinal Medications - Concurrent administration of either calcium carbonate or aluminium and magnesium-hydroxide containing antacids does not alter the initial absorption or systemic exposure (AUC_{0-t}) of raloxifene. In the osteoporosis treatment trial, co-

administered gastrointestinal medications (including bisacodyl, cisapride, docusate, H₂-antagonists, laxatives, loperamide, omeprazole and psyllium) had no effect on plasma raloxifene concentration.

Highly glucuronidated drugs – The influence of co-administered highly glucuronidated drugs (including paracetamol, ketoprofen, morphine and oxazepam) on raloxifene plasma concentrations was evaluated in the osteoporosis treatment trial. No clinically significant effects of these agents on raloxifene plasma concentrations were identified.

Highly protein-bound drugs – The influence of co-administered highly protein-bound drugs (including diazepam, gemfibrozil, ibuprofen, naproxen and warfarin) on raloxifene plasma concentrations was evaluated in the osteoporosis treatment trial. No clinically significant effects of these agents on raloxifene plasma concentrations were identified. In vitro, raloxifene did not affect the binding of phenytoin, tamoxifen or warfarin. As small decreases in the prothrombin time have been observed with raloxifene, if raloxifene is given concurrently with warfarin or other coumarin derivatives, the prothrombin time should be monitored.

Hormones - Raloxifene increases hormone-binding globulin concentrations, including sex steroid binding globulins (SHBG), thyroxine binding globulin (TBG), and corticosteroid binding globulin (CBG), with corresponding increases in total hormone concentrations. These changes do not affect concentrations of free hormones.

Lipid-lowering drugs - Raloxifene lowers serum total and LDL cholesterol but does not affect serum concentrations of total HDL cholesterol or triglycerides. These effects should be taken into account in therapeutic decisions for patients who may require therapy for hyperlipidaemia. Concurrent use of raloxifene and lipid-lowering agents has not been studied.

Concomitant use of oestrogens – In the clinical trial program, there were no interactions noted with concomitant use of vaginal oestrogen preparations and raloxifene (see PRECAUTIONS).

ADVERSE EFFECTS

Osteoporosis Treatment Clinical Trial

Therapy was discontinued due to an adverse event in 10.9% of women treated with raloxifene hydrochloride 60 mg and 8.8% of women treated with placebo. Common adverse reactions considered to be related to EVIFYNE therapy were hot flushes and leg cramps. Hot flushes were most commonly reported during the first 6 months of treatment and were not different from placebo thereafter.

Osteoporosis Prevention Clinical Trial

The adverse event most frequently reported as the reason for discontinuation in patients treated with raloxifene was hot flushes. Discontinuation rates due to hot flushes did not differ significantly between raloxifene and placebo groups (1.7% and 2.2%, respectively).

Osteoporosis Treatment and Prevention Clinical Trials

Across all placebo-controlled clinical trials of raloxifene in osteoporosis, venous thromboembolic events, including deep vein thrombosis, pulmonary embolism and retinal

vein thrombosis occurred in a frequency of approximately 0.7 % or 3.25 cases per 1,000 patient years. A relative risk of 2.32 (CI 1.26, 4.26) was observed in raloxifene treated patients compared to placebo. The risk of a thromboembolic event was greatest in the first four months of therapy. Superficial vein thrombophlebitis occurred in a frequency of less than 1%.

Table 6 lists adverse events occurring in either the osteoporosis treatment or the prevention placebo-controlled clinical trial databases at a frequency $\geq 2.0\%$ in either group and in more raloxifene-treated women than in placebo-treated women. Adverse events are shown without attribution of causality.

Table 6. Adverse events occurring in placebo-controlled osteoporosis clinical trials at a frequency $\geq 2.0\%$ and in more raloxifene hydrochloride-treated (60 mg once daily) women than placebo-treated women

Body System	Treatment		Prevention	
	Raloxifene N=2557 %	Placebo N=2576 %	Raloxifene N=581 %	Placebo N=584 %
<i>Body as a Whole</i>				
Infection	A	A	15.1	14.6
Flu Syndrome	13.5	11.4	14.6	13.5
Headache	9.2	8.5	A	A
Leg Cramps	7.0	3.7	5.9	1.9
Chest Pain	A	A	4.0	3.6
Fever	3.9	3.8	3.1	2.6
<i>Cardiovascular System</i>				
Hot Flushes	9.7	6.4	24.6	18.3
Migraine	A	A	2.4	2.1
Syncope	2.3	2.1	B	B
Varicose Vein	2.2	1.5	B	B
<i>Digestive System</i>				
Nausea	8.3	7.8	8.8	8.6
Diarrhoea	7.2	6.9	A	A
Dyspepsia	A	A	5.9	5.8
Vomiting	4.8	4.3	3.4	3.3
Flatulence	A	A	3.1	2.4
Gastrointestinal Disorder	A	A	3.3	2.1
Gastroenteritis	B	B	2.6	2.1
<i>Metabolic and Nutritional</i>				
Weight Gain	A	A	8.8	6.8
Peripheral Oedema	5.2	4.4	3.3	1.9
<i>Musculoskeletal System</i>				
Arthralgia	15.5	14.0	10.7	10.1
Myalgia	A	A	7.7	6.2
Arthritis	A	A	4.0	3.6
Tendon Disorder	3.6	3.1	A	A

<i>Nervous System</i>				
Depression	A	A	6.4	6.0
Insomnia	A	A	5.5	4.3
Vertigo	4.1	3.7	A	A
Neuralgia	2.4	1.9	B	B
Hypaesthesia	2.1	2.0	B	B
<i>Respiratory System</i>				
Sinusitis	7.9	7.5	10.3	6.5
Rhinitis	10.2	10.1	A	A
Bronchitis	9.5	8.6	A	A
Pharyngitis	5.3	5.1	7.6	7.2
Cough Increased	9.3	9.2	6.0	5.7
Pneumonia	A	A	2.6	1.5
Laryngitis	B	B	2.2	1.4
<i>Skin and Appendages</i>				
Rash	A	A	5.5	3.8
Sweating	2.5	2.0	3.1	1.7
<i>Special Senses</i>				
Conjunctivitis	2.2	1.7	B	B
<i>Urogenital System</i>				
Vaginitis	A	A	4.3	3.6
Urinary Tract Infection	A	A	4.0	3.9
Cystitis	4.6	4.5	3.3	3.1
Leukorrhoea	A	A	3.3	1.7
Uterine Disorder ^{a,b}	2.5	1.8	A	A
Endometrial Disorder ^a	B	B	3.1	1.9
Vaginal Haemorrhage	2.5	2.4	A	A
Urinary Tract Disorder	2.5	2.1	A	A

A Placebo incidence greater than or equal to raloxifene hydrochloride 60 mg incidence

B Less than 2% incidence and more frequent with raloxifene hydrochloride 60 mg

a Treatment-emergent uterine-related adverse event, including only patients with an intact uterus:
Prevention Trials: raloxifene hydrochloride 60 mg, n=354, Placebo, n=364; Treatment Trial:
raloxifene hydrochloride 60 mg, n=1948, Placebo, n=1999.

b Actual terms most frequently referred to endometrial fluid.

Comparison of Raloxifene Hydrochloride 60 mg and Hormone Replacement Therapy

Raloxifene hydrochloride 60 mg was compared with oestrogen-progestin replacement therapy (HRT) in 3 clinical trials for prevention of osteoporosis. Table 7 shows adverse events occurring more frequently in one treatment group and at an incidence $\geq 2.0\%$ in any group. Adverse events are shown without attribution of causality.

Table 7. Adverse events reported in the clinical trials for osteoporosis prevention with raloxifene hydrochloride (60 mg once daily) and continuous combined or cyclic oestrogen plus progestin (HRT) at an incidence $\geq 2.0\%$ in any treatment group^a

Adverse Event	Raloxifene	HRT- Continuous Combined	HRT-Cyclic
	(N=317) %	(N=96) %	(N=219) %
<i>Urogenital</i>			
Breast Pain	4.4	37.5	29.7
Vaginal Bleeding ^b	6.2	64.2	88.5
<i>Digestive</i>			
Flatulence	1.6	12.5	6.4
<i>Cardiovascular</i>			
Hot flushes	28.7	3.1	5.9
<i>Body as a Whole</i>			
Infection	11.0	0	6.8
Abdominal Pain	6.6	10.4	18.7
Chest Pain	2.8	0	0.5

^a These data are from both blinded and open-label studies.

^b Treatment-emergent uterine-related adverse event, including only patients with an intact uterus: raloxifene hydrochloride 60 mg, n=290, HRT-Continuous Combined, n=67, HRT-Cyclic, n=217.

Continuous Combined HRT = 0.625 mg conjugated oestrogens plus 2.5 mg medroxyprogesterone acetate.

Cyclic HRT = 0.625 mg conjugated oestrogens for 28 days with concomitant 5 mg medroxyprogesterone acetate or 0.15 mg norgestrel on days 1 through 14 or 17 through 28.

Breast Pain

Across all placebo-controlled trials, EVIFYNE was indistinguishable from placebo with regard to frequency and severity of breast pain and tenderness. EVIFYNE was associated with less breast pain and tenderness than reported by women receiving estrogens with or without added progestin.

Gynaecologic Cancers

EVIFYNE-treated and placebo-treated groups had similar incidences of endometrial cancer and ovarian cancer.

Placebo-Controlled Trial of Postmenopausal Women at Increased Risk for Major Coronary Events (RUTH)

The safety of EVIFYNE (60 mg once daily) was assessed in a placebo-controlled multinational trial of 10,101 postmenopausal women (age range 55–92) with documented coronary heart disease (CHD) or multiple CHD risk factors. Median study drug exposure was 5.1 years for both treatment groups (*see CLINICAL TRIALS*). Therapy was discontinued due to an adverse reaction in 25% of 5044 EVIFYNE-treated women and 24% of 5057 placebo treated women. The incidence per year of all-cause mortality was similar between the raloxifene (2.07%) and placebo (2.25%) groups.

Adverse reactions reported more frequently in EVIFYNE-treated women than in placebo-treated women included peripheral oedema (14.1% raloxifene versus 11.7% placebo), muscle

spasms/leg cramps (12.1% raloxifene versus 8.3% placebo), hot flushes (7.8% raloxifene versus 4.7% placebo), venous thromboembolic events (2.0% raloxifene versus 1.4% placebo), and cholelithiasis (3.3% raloxifene versus 2.6% placebo).

Tamoxifen-Controlled Trial of Postmenopausal Women at Increased Risk for Invasive Breast Cancer (STAR)

The safety of EVIFYNE 60 mg/day versus tamoxifen 20 mg/day over 5 years was assessed in 19,747 postmenopausal women (age range 35-83 years) in a randomised, double-blind trial. As of 31 December 2005, the median follow-up was 4.3 years. The safety profile of raloxifene was similar to that in the placebo-controlled raloxifene trials.

DOSAGE AND ADMINISTRATION

The recommended dosage is one 60 mg EVIFYNE tablet per day orally, which may be taken at any time of day without regard to meals. No dose adjustment is necessary for the elderly.

Supplemental calcium should be added to the diet if daily intake is inadequate.

There are no data on the discontinuation effects of EVIFYNE. Raloxifene exerts its effect through the oestrogen receptor and does not accumulate in any target tissue. Therefore, continuous daily treatment with EVIFYNE is required to maintain the effect of the drug.

Concomitant use of oestrogens – see PRECAUTIONS.

OVERDOSAGE

In clinical trials, no overdose of raloxifene has been reported. In an 8-week study of 63 postmenopausal women, a dose of raloxifene hydrochloride of 600 mg/day was safely tolerated. In clinical trials, more than 2500 post-menopausal women received a daily dose of 120 mg for three years.

In postmarketing spontaneous reports, overdose has been reported very rarely (less than 1 out of 10000 [$<0.01\%$] patients treated). The highest overdose has been approximately 1.5 grams. No fatalities associated with overdose have been reported. In adults, symptoms reported in patients who took more than 120mg as a single ingestion included leg cramps and dizziness. In some cases, no adverse events were reported as a result of the overdose.

Raloxifene is not indicated for use in children, however, in accidental overdose in children under 2 years of age, the maximum reported dose has been 180mg. In children, symptoms reported included ataxia, dizziness, vomiting, rash, diarrhoea, tremor and flushing, as well as elevation in alkaline phosphatase.

No mortality was seen after a single oral dose in rats or mice at 5000 mg/kg (810 times the human dose for rats and 405 times the human dose for mice based on surface area, mg/m^2) or in monkeys at 1000 mg/kg (80 times the AUC in humans).

There is no specific antidote for raloxifene.

PRESENTATION AND STORAGE CONDITIONS

EVIFYNE tablets containing 60 mg raloxifene hydrochloride (equivalent to 56 mg raloxifene) are available in packs of 7 (sample pack) and 28. Store below 30°C in a dry place. Do not freeze and protect from excessive heat and sunlight.

Shelf life: 2 years

Incompatibilities: Not applicable

NAME AND ADDRESS OF THE SPONSOR

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POISONS SCHEDULE

S4 – Prescription only medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

15 November 2010

DATE OF MOST RECENT AMENDMENT

01 November 2012