SCHEDULING STATUS:

Schedule 3

PROPRIETARY NAME AND DOSAGE FORM:

EVISTA Tablets

COMPOSITION:

Each film-coated tablet contains raloxifene hydrochloride 60 mg.

It also contains povidone, polysorbate 80, anhydrous lactose, lactose monohydrate, crospovidone, magnesium stearate, titanium dioxide (E 171), hypromellose, macrogol 400, carnauba wax, shellac, propylene glycol and indigo carmine (E 132).

PHARMACOLOGICAL CLASSIFICATION:

A 34 Other

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Raloxifene is a non-steroidal benzothiophene derivative which acts as a Selective Oestrogen Receptor Modulator (SERM). The selective profile of raloxifene includes oestrogen agonist effects on bone and lipids and oestrogen antagonist effects in breast and uterine tissues.

Skeletal effects: Raloxifene reduces the resorption of bone and decreases overall bone turnover. In clinical trials in women who were 2 to 8 years postmenopausal, raloxifene 60 mg per day produced significant increases in bone mineral density (BMD) of hip and spine as well as total body mineral mass compared to placebo. Bone quality was maintained during these trials. Treatment with raloxifene for three years in postmenopausal women with a mean age of 66 years and with osteoporosis reduced the incidence of vertebral fractures.

Effects on lipid metabolism: In clinical trials, raloxifene decreased serum total cholesterol and LDL cholesterol without significant effects on serum total HDL cholesterol or triglycerides. Raloxifene

increased serum HDL-2 cholesterol and apolipoprotein A_1, while serum fibrinogen, apolipoprotein B and lipoprotein(a) were decreased.

Effects on the endometrium: Raloxifene was not associated with endometrial thickening (see 'Special Precautions').

Effects on breast tissue: Raloxifene has no stimulatory effect on breast tissue. Across all placebo-controlled trials, raloxifene was indistinguishable from placebo with regard to frequency and severity of breast symptoms.

A reduction in the risk to develop invasive breast cancer has been reported in postmenopausal women with osteoporosis who were treated with raloxifene.

The reduction in the risk to develop breast cancer is not applicable to oestrogen receptor negative (ER-) cancers and cancers of unknown oestrogen receptor status.

Pharmacokinetic properties:

Absorption: Approximately 60 % of an oral dose is absorbed. Pre-systemic glucuronidation is extensive. Absolute bioavailability of raloxifene is 2 %.

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

Raloxifene and the monoglucuronide conjugates are highly bound to plasma proteins, including both albumin and α-1-acid-glycoprotein.

Metabolism: Raloxifene undergoes extensive first pass metabolism to glucuronide conjugates. Raloxifene levels are maintained by enterohepatic recycling, giving a plasma half-life of 27,7 hours.

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

Special populations:

Renal insufficiency: See 'Excretion' above.

Hepatic insufficiency:

Raloxifene is metabolised primarily in the liver. Safety and efficacy of raloxifene has not been studied in patients with impaired liver function. Raloxifene was studied as a single dose in patients with Child-Pugh Class A cirrhosis with a total serum bilirubin ranging from 10,3 to 34,2 µmol/L. Plasma concentrations were approximately 2,5 times higher than in controls and correlated with total bilirubin concentrations.

INDICATIONS:

EVISTA is indicated for the prevention and treatment of osteoporosis in postmenopausal women.
Clinical studies have shown a reduction in the incidence of non-traumatic vertebral fractures. The effects of EVISTA on the risk for extra-vertebral fractures are not known.
To reduce the risk of development of invasive breast cancer in postmenopausal women with osteoporosis.
The risk reduction is not applicable to oestrogen receptor negative (ER-) cancers and cancers of unknown oestrogen receptor status.

CONTRAINDICATIONS:

Hypersensitivity to raloxifene or to any other components of EVISTA.

Active or past history of venous thromboembolic events (VTE), including deep vein thrombosis, pulmonary embolism and retinal vein thrombosis.
Liver cirrhosis (see Special Precautions).
Pregnancy and Lactation (see PREGNANCY AND LACTATION).

WARNINGS AND SPECIAL PRECAUTIONS:

In a study of postmenopausal women with documented coronary heart disease or at increased risk for coronary events taking EVISTA, the incidence of stroke, myocardial infarction, hospitalised acute coronary syndrome, cardiovascular mortality, or overall mortality was comparable to placebo. However, there was an increase in mortality due to stroke. The incidence of stroke mortality was 1,5 per 1 000 women per year for placebo versus 2,2 per 1 000 women per year for EVISTA.

The risk-benefit balance of EVISTA 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 EVISTA.

EVISTA should be discontinued in the event of an illness or a condition leading to a prolonged period of immobilisation. Discontinuation should happen as soon as possible in case of the illness or from three days before the immobilisation occurs. Therapy should not be restarted until the initiating condition has resolved and the patient is fully mobile. (See CONTRAINDICATIONS - VTE)

EVISTA should not be prescribed for the relief of vasomotor symptoms (hot flushes). It should only be used in postmenopausal women (absence of periods for 12 months).

EVISTA should not be used in patients with endometrial cancer as safety in this patient group has not been proven.

Treatment of mice and rats with EVISTA was associated with an increased risk of the development of benign and malignant ovarian tumours. The female rodents in these studies were treated during their reproductive lives, when their ovaries were functional and highly responsive to hormonal stimulation. In contrast to the highly responsive ovaries in this rodent model, the human ovary after menopause is relatively unresponsive to reproductive stimulation. The relevance of this finding in humans is currently unknown. EVISTA was not genotoxic in any of the extensive battery of test systems applied.

Any uterine bleeding during EVISTA therapy is unexpected and should be fully investigated (see Pharmacodynamic properties).

The safety of EVISTA in patients with breast cancer has not been adequately studied. No data are available on the concomitant use of EVISTA and agents used in the treatment of early or advanced breast cancer.

In patients with a history of oral oestrogen-induced hypertriglyceridaemia (>5,6 mmol/L), EVISTA may be associated with a marked increase in serum triglycerides. Patients with this medical history should have serum triglycerides monitored when taking EVISTA.

Until safety and efficacy have been evaluated further in patients with hepatic insufficiency, the use of EVISTA is not recommended in this patient population (see Pharmacokinetic properties).

Cases of moderate increases in AST and/or ALT have been reported where a causal relationship to EVISTA cannot be excluded.

EVISTA contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

INTERACTIONS:

EVISTA should not be co-administered with cholestyramine which significantly reduces the absorption and therefore the enterohepatic cycling of EVISTA.

Antacids containing calcium carbonate or aluminium and magnesium-hydroxide do not affect the systemic availability of EVISTA.

Co-administration of EVISTA and warfarin may decrease prothrombin time modestly. In such cases, prothrombin time should be monitored.

In vitro, EVISTA did not interact with the binding of warfarin, phenytoin, or tamoxifen. EVISTA has no effect on the pharmacokinetics of digoxin.

The chronic administration of EVISTA has no effect on the pharmacokinetics of methylprednisolone administered as a single oral dose.

In clinical trials, no interaction was noted with paracetamol, non-steroidal anti-inflammatory medicines (such as aspirin, ibuprofen and naproxen), oral antibiotics, H_1 antagonists, H_2 antagonists and benzodiazepines.

Peak concentrations of EVISTA are reduced with co-administration of ampicillin. However, since the overall extent of absorption and the elimination rate of EVISTA are not affected, EVISTA can be concurrently administered with ampicillin.

Concomitant use of vaginal oestrogen preparations was allowed in the clinical trial programme. No interaction was noted and compared to placebo there was no increased use in EVISTA-treated patients.

Safety information regarding the concurrent use of EVISTA and systemic hormone therapy (oestrogen without progesterone) is limited and therefore concomitant use of EVISTA with systemic oestrogen is not recommended.

EVISTA modestly increases hormone-binding globulin concentrations, including sex steroid binding globulin, thyroxine binding globulin and corticosteroid binding globulin, with corresponding increases in measured total hormone concentration. There is no evidence that these changes affect concentrations of the corresponding free hormones.

PREGNANCY AND LACTATION:

Pregnancy

EVISTA must not be used in women of child-bearing potential. If EVISTA is used during pregnancy it may be associated with an increased risk of congenital defects in the foetus. If it is used mistakenly during pregnancy or the patient becomes pregnant while taking EVISTA, the patient should be informed of the potential hazard to the foetus (see CONTRAINDICATIONS).

Lactation

It is not known whether EVISTA is excreted in human milk. Its clinical use, therefore, cannot be recommended in lactating women. EVISTA may affect the development of the baby (see CONTRAINDICATIONS).

DOSAGE AND DIRECTIONS FOR USE:

The recommended dosage is one 60 mg EVISTA tablet daily by oral administration, which may be taken at any time of day without regard to meals. No dose adjustment is necessary for the elderly.
Women receiving EVISTA should be given supplements of calcium if the daily intake is less than 800 mg per day.

SIDE EFFECTS:

The following table summarises the core adverse drug reaction terms and their frequencies identified during placebo-controlled osteoporosis clinical trials:

System Organ Class/Adverse Event	**Very common ≥1:10 (≥10 %)**	**Common ≥1:100 and <1:10 (≥1 % and <10 %)**	**Uncommon ≥1:1 000 and <1:100 (≥0,1 % and <1 %)**	**Rare ≥1/10 000 and <1:1 000 (≥0,01 % and <0,1 %)**	**Very rare <1:10 000 (<0,01 %)**
Vascular Disorders					
Vasodilatation (hot	X				

System Organ Class/Adverse Event	Very common ≥1:10 (≥10 %)	Common ≥1:100 and <1:10 (≥1 % and <10 %)	Uncommon ≥1:1 000 and <1:100 (≥0,1 % and <1 %)	Rare ≥1/10 000 and <1:1 000 (≥0,01 % and <0,1 %)	Very rare <1:10 000 (<0,01 %)
flushes)					
Venous thromboembolytic events (including deep vein thrombosis, pulmonary embolism, retinal vein thrombosis, superficial vein thrombophlebitis)			X		
General Disorders and Administration Site Conditions					
Peripheral oedema		X			
Musculoskeletal and Connective Tissue Disorders					
Leg cramps		X			

Table 1. Frequency of venous thromboembolism in raloxifene-treated patients (60mg/day) across placebo-controlled trials of at least 6 months in duration.

Clinical Trial	Frequency Raloxifene	Frequency Placebo

Postmenopausal women: osteoporosis treatment and prevention clinical trials	3,05/1 000 patient-years (0,9 % cumulative incidence)[a]	0,81/1 000 patient-years (0,2 % cumulative incidence)[a]
Postmenopausal women: documented coronary heart disease or at increased risk for coronary events	3,88/1 000 patient-years (2,0 % cumulative incidence)[b]	2,70/1 000 patient-years (1,4 % cumulative incidence)[b]

[a] Median duration of exposure was 42 months.

[b] Median duration of exposure was 61 months.

Table 2. Frequency of adverse reactions in placebo-controlled clinical trials (raloxifene 60 mg/day).

Term	Osteoporosis Treatment Frequency (%)	Osteoporosis Prevention Frequency (%)
Vasodilatation/ hot flush	9,7	24,3
Superficial thrombophlebitis	1,3	0,2[a]
Leg cramps/ muscle spasms	7,0	5,5
Peripheral oedema	5,2	3,1
Cholelithiasis	1,5[b]	1,0[b]

[a] Reported for 1 Raloxifene-treated patient.

[b] Raloxifene did not separate statistically from placebo in the osteoporosis treatment and prevention clinical trials.

Post-Marketing Surveillance data:

In post-marketing surveillance, adverse events that have been reported in patients taking EVISTA include:

Gastrointestinal: Nausea, abdominal pain, vomiting and dyspepsia.

Skin and Subcutaneous tissue: Rash.

Decreased platelet counts have been reported during EVISTA treatment.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

In post-marketing spontaneous reports, overdose has been reported very rarely (less than 1 out of 10 000 [<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 120 mg as a single ingestion included leg cramps and dizziness. In some cases, no adverse events were reported as a result of the overdose.

In accidental overdose in children under 2 years of age, the maximum reported dose has been 180 mg.

In children, symptoms reported included ataxia, dizziness, vomiting, rash, diarrhoea, tremor and flushing, as well as elevation in alkaline phosphatase.

There is no specific antidote for EVISTA. Treatment is symptomatic and supportive.

IDENTIFICATION:

EVISTA (Tablets), TA 4165, are white, film-coated, elliptically shaped tablets, which are imprinted with 4165 in blue ink.

PRESENTATION:

EVISTA (Tablets) are supplied in blister packs of 28. The blister pack consists of PVC/PE/PCTFE blisters with aluminium foil lidding.

STORAGE INSTRUCTIONS:

Store at or below 30 ºC.

EVISTA tablets should not be exposed to excessive heat or sunlight.

Keep out of reach of children.

REGISTRATION NUMBER:

32/34/0422

NAME AND BUSINESS ADDRESS OF THE APPLICANT:

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