EXETAS 25 MG TABLET

Exemestane Tablets 25 mg

Composition:
Each film coated tablet contains:
Exemestane 25 mg

Dosage form: Tablet

Product Description
White to off –white , round, biconvex film coated tablets debossed with 'E25' on one side and plain on the other.

Pharmacodynamic properties
Pharmacotherapeutic group: steroidal aromatase inhibitor; anti-neoplastic agent
ATC: L02BG06

Exemestane is an irreversible, steroidal aromatase inhibitor, structurally related to the natural substrate androstenedione. In post-menopausal women, oestrogens are produced primarily from the conversion of androgens into oestrogens through the aromatase enzyme in peripheral tissues. Oestrogen deprivation through aromatase inhibition is an effective and selective treatment for hormone dependent breast cancer in postmenopausal women. In postmenopausal women, Exemestane p.o. significantly lowered serum oestrogen concentrations starting from a 5 mg dose, reaching maximal suppression (>90%) with a dose of 10-25 mg. In postmenopausal breast cancer patients treated with the 25 mg daily dose, whole body aromatization was reduced by 98%.

Exemestane does not possess any progestogenic or oestrogenic activity. A slight androgenic activity, probably due to the 17-hydro derivative, has been observed mainly at high doses. In multiple daily doses trials, Exemestane had no detectable effects on adrenal biosynthesis of cortisol or aldosterone, measured before or after ACTH challenge, thus demonstrating its selectivity with regard to the other enzymes involved in the steroidogenic pathway. Glucocorticoid or mineralocorticoid replacement are therefore not needed.

Pharmacokinetic properties
Absorption:
After oral administration of Exemestane tablets, exemestane is absorbed rapidly. The fraction of the dose absorbed from the gastrointestinal tract is high. The absolute bioavailability in humans is unknown, although it is anticipated to be limited by an extensive first pass effect. A similar effect resulted in an absolute bioavailability in rats and dogs of 5%. After a single dose of 25 mg, maximum plasma levels of 18ng/ml are reached after 2 hours. Concomitant intake with food increases the bioavailability by 40%.

Distribution:
The volume of distribution of exemestane, not corrected for the oral bioavailability, is ca 20000 l. The kinetics is linear and the terminal elimination half-life is 24 h. Binding to plasma proteins is 90% and is concentration independent. Exemestane and its metabolites do not bind to red blood cells.
Exemestane does not accumulate in an unexpected way after repeated dosing.

Metabolism and excretion:
Exemestane is metabolised by oxidation of the methylene moiety on the 6 position by CYP 3A4 isoenzyme and/or reduction of the 17-keto group by aldoketoreductase followed by conjugation. The clearance of exemestane is ca 500 l/h, not corrected for the oral bioavailability.
The metabolites are inactive or the inhibition of aromatase is less than the parent compound.
The amount excreted unchanged in urine is 1% of the dose. In urine and faeces equal amounts (40%) of ^{14}C-labeled exemestane were eliminated within a week.

Special populations
Age: No significant correlation between the systemic exposure of Exemestane and the age of subjects has been observed.

Renal insufficiency:
In patients with severe renal impairment (CL_{cr} < 30 ml/min) the systemic exposure to exemestane was 2 times higher compared with healthy volunteers.
Given the safety profile of exemestane, no dose adjustment is considered to be necessary.

Hepatic insufficiency:.
In patients with moderate or severe hepatic impairment the exposure of exemestane is 2-3 fold higher compared with healthy volunteers. Given the safety profile of exemestane, no dose adjustment is considered to be necessary.

Indication/Usage
Exemestane is indicated for the adjuvant treatment of postmenopausal women with estrogen receptor positive early breast cancer who have received two to three years of Tamoxifen and are switched to Exemestane for completion of a total of five consecutive years of adjuvant hormonal therapy.

Exemestane is indicated for the treatment of advanced breast cancer in women with natural or induced postmenopausal status whose disease has progressed following anti-estrogen therapy alone.

Exemestane is also indicated for the treatment of post-menopausal woman with advanced breast cancer whose disease has progressed following multiple hormonal therapies.

Efficacy has not been demonstrated in patients with estrogen receptor negative status.

Recommended Dose
Adult and elderly patients
The recommended dose of Exemestane is one 25 mg tablet to be taken once a day-after a meal.

In patients with early breast cancer, treatment with Exemestane should continue until completion of five years of combined sequential adjuvant hormonal therapy (tamoxifen followed by Exemestane), or earlier if tumour relapse occurs.

In patients with advanced breast cancer, treatment with Exemestane should continue until tumour progression is evident.

No dose adjustments are required for patients with hepatic or renal insufficiency.

Children
Not recommended for use in children.

Route of Administration
Oral Use.

Contraindication
Exemestane tablets are contraindicated in patients with a known hypersensitivity to the active substance or to any of the excipients, in pre-menopausal women and in pregnant or lactating women.

Warnings & Precaution
Because of its mode of action, exemestane should not be administered to women with pre-menopausal endocrine status.

Exemestane should not be co-administered with estrogen-containing medicines as these would negate its pharmacological action.

As exemestane is a potent estrogen lowering agent, reductions in bone mineral density can be anticipated. During adjuvant treatment with exemestane, women with osteoporosis or at risk of osteoporosis should have their bone mineral density formally assessed by bone densitometry at the commencement of treatment. Patients treated with exemestane should be carefully monitored and treatment for osteoporosis should be initiated as appropriate.

Interaction with other medicaments
Exemestane should be used cautiously with drugs that are metabolised via CYP3A4 and have a narrow therapeutic window. There is no clinical experience of the concomitant use of Exemestane with other anticancer drugs.

Exemestane should not be coadministered with oestrogen-containing medicines as these would negate its pharmacological action.

Pregnancy and Lactation

Pregnancy

No clinical data on exposed pregnancies are available with Exemestane. Studies on animals have shown reproductive toxicity. Exemestane is therefore contraindicated in pregnant women.

Lactation

It is not known whether exemestane is excreted into human milk. Exemestane should not be administered to lactating woman.

Women of perimenopausal status or child-bearing potential

The physician needs to discuss the necessity of adequate contraception with women who have the potential to become pregnant including women who are perimenopausal or who have recently become postmenopausal, until their postmenopausal status is fully established.

Side effects/Adverse Reactions

Most adverse reactions can be attributed to the normal pharmacological consequences of estrogen deprivation (eg hot flushes).

The reported adverse reactions are listed below by MedDRA system organ class and by frequency.

Frequencies are defined as: very common (≥1/10) common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000)

Metabolism and nutrition disorders:	
Common	Anorexia
Psychiatric disorders:	
Very common	Depression ,Insomnia
Nervous system disorders:	
Very common	Headache, Dizziness
Common	carpal tunnel syndrome
Vascular disorders:	
Very common	Hot flushes
Gastrointestinal disorders:	
Very common	Abdominal pain ,Nausea
Common	vomiting, constipation, dyspepsia,diarrhoea
Hepatobiliary disorders:	
Very Common	Hepatic Enzyme increased, blood bilirubin increased, K Phosphatase increased.
Skin and subcutaneous tissue disorders:	
Very common	Increased sweating
Common	Rash, alopecia
Musculoskeletal and bone disorders:	
Very common	Joint and musculoskeletal pain (*)
Common	Osteoporosis, fracture
General disorders and administration site conditions:	
Very common	Pain ,Fatigue
Common	Oedema peripheral

(*) Includes: arthralgia, and less frequently pain in limb, osteoarthritis, back pain, arthritis, myalgia and joint stiffness

Signs & Symptoms of overdose and Treatment

There is no specific antidote to overdosage and treatment must be symptomatic. General supportive care, including frequent monitoring of vital signs and close observation of the patient, is indicated.

Storage Conditions: Store below 30°C.

Shelf life: 24 Months

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