SCHEDULING STATUS

S5

PROPRIETARY NAME AND DOSAGE FORM

NYXE 5 mg (Tablet)

NYXE 10 mg (Tablet)

COMPOSITION

NYXE 5 mg: Each film-coated tablet contains 5 mg zolpidem tartrate. Contains 43.8 mg lactose.

NYXE 10 mg: Each film-coated tablet contains 10 mg zolpidem tartrate. Contains 87.6 mg lactose.

The inactive ingredients are hypromellose, macrogol 400, magnesium stearate, microcrystalline cellulose, sodium starch glycolate and titanium dioxide (C.I. No: 77891).

PHARMACOLOGICAL CLASSIFICATION

A 2.2 Sedatives, hypnotics

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Zolpidem is an imidazopyridine compound with sedative/hypnotic effects. It has a potent agonist effect on the benzodiazepine receptor component of the gamma-aminobutyric acid (GABA) receptor complex, modulating the opening of the chloride ion channel. Zolpidem possesses relative selectivity for the omega-1 (benzodiazepine-1) $GABA_A$ receptor.

Pharmacokinetic properties

Absorption is rapid and complete, although first pass metabolism results in a bioavailability of 70 % after oral administration. Simultaneous intake of food may decrease the rate and extent of absorption. Peak plasma concentrations are reached within 0,5 to 3 hours after dosing. Zolpidem is highly protein bound (92 %) and the elimination half-life is approximately 2,5 hours. This may be prolonged in the elderly and in patients with hepatic or renal impairment. Zolpidem is metabolised in the liver to inactive metabolites which are excreted in the urine (56 %) and faeces (37 %).

INDICATIONS

NYXE is indicated for the short-term treatment of insomnia, when the disorder is severe, disabling or subjecting the individual to extreme distress.

CONTRAINDICATIONS

Hypersensitivity to zolpidem or any components of the formulation.

Pulmonary disease, severe chronic obstructive, as respiratory failure may be precipitated.

Sleep apnoea syndrome

Severe hepatic insufficiency

Myasthenia gravis

HIV protease inhibitors such as ritonavir: May increase plasma concentrations of NYXE with a risk of extreme sedation and respiratory depression. Concomitant administration is not recommended. (SEE INTERACTIONS).

Children under the age of 18.

Pregnancy and lactation. (See PREGNANCY AND LACTATION).

WARNINGS and SPECIAL PRECAUTIONS

NYXE may lead to drowsiness and impaired concentration, which may be aggravated by simultaneous intake of alcohol or other central nervous system depressants. See “Effects on ability to drive and use machines”.

NYXE should not be used to treat depression or anxiety with depression as suicide may be precipitated in these patients.

Pre-existing depression may be unmasked during therapy with NYXE.

Elderly patients may be more likely to experience confusion or falls while taking NYXE.

NYXE should be used with caution in patients with a history of drug or alcohol abuse as a predisposition to dependence may exist. (See Special precautions).

Porphyria: Safety has not been established.

Dependence – There is a potential for abuse and the development of physical and psychological dependence, especially with prolonged use and high doses. Abuse has been reported in polydrug users. Once physical dependence has developed, abrupt termination of therapy may result in a withdrawal syndrome presenting with headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis (abnormal acute hearing),

numbness and tingling of extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

Duration of treatment – The duration of treatment should be as short as possible, but should not exceed four weeks including the tapering-off process (See DOSAGE AND DIRECTIONS FOR USE). Extension beyond this period should not take place without re-evaluation of the patient.

Some loss of efficacy of NYXE may develop after repeated use.

NYXE contains lactose and should not be administered to patients with rare hereditary problems, or a history of lactose intolerance, Lapp lactose deficiency or glucose-galactose malabsorption.

Effects on ability to drive and use machines

NYXE may lead to drowsiness and impaired concentration, which may be aggravated by simultaneous intake of alcohol or other central nervous system depressants. Patients should be warned against driving motor vehicles or operating machinery or performing potentially hazardous tasks where loss of concentration may lead to accidents.

INTERACTIONS

Alcohol: Concomitant use may enhance the sedative effect of NYXE.

Central Nervous System (CNS) depressant medicines: Concurrent use with NYXE may produce additive CNS depressant effects. Euphoria may be enhanced when NYXE is used concurrently with narcotic analgesics and this may increase psychological dependence.

Hepatic enzyme inhibitors including erythromycin and cimetidine: Inhibitors of cytochrome P450 enzymes may increase the plasma levels of NYXE. Inducers of the cytochrome P450 enzymes (e.g. rifampicin) may decrease the levels of NYXE.

HIV protease inhibitors such as ritonavir: May increase plasma concentrations of NYXE with a risk of extreme sedation and respiratory depression. Concomitant administration is not recommended (SEE CONTRA-INDICATIONS).

Antidepressants including bupropion, fluoxetine, desipramine, sertraline and venlafaxine: Hallucinations have been reported with concurrent use of NYXE and certain antidepressants.

Warfarin, digoxin, ranitidine or itraconazole: no significant pharmacokinetic interactions were observed with concurrent administration of NYXE.

Chlorpromazine: Concurrent use may prolong elimination half-life of chlorpromazine.

Imipramine: Concurrent use may increase drowsiness and incidence of anterograde amnesia and decrease peak concentrations of imipramine.

PREGNANCY AND LACTATION

Safety and efficacy in pregnancy and lactation have not been established.

Chronic maternal use of sedatives/hypnotics has been associated with withdrawal symptoms in infants.

NYXE is distributed in small amounts into breast milk and is therefore not recommended for breastfeeding mothers.

DOSAGE AND DIRECTIONS FOR USE

Treatment should be started with the lowest recommended dose. The maximum dose should not be exceeded.

Safety and efficacy in children under the age of 18 years has not been established. (See CONTRAINDICATIONS).

Adults: 10 mg immediately before retiring or in bed.

Geriatric or debilitated patients and patients with impaired hepatic function: A lower dose of 5 mg should be used initially in these patients.

The total daily dose of NYXE should not exceed 10 mg.

Duration of treatment: NYXE therapy should be for as short a time as possible (a few days to two weeks with a maximum of four weeks including the tapering off process). Use for any longer periods requires re-evaluation of the patient. Prolonged treatment requires that NYXE be gradually tapered to prevent withdrawal symptoms. (See WARNINGS and SPECIAL PRECAUTIONS).

SIDE EFFECTS

Nervous system disorders:

Less frequent: Daytime drowsiness, confusion, mental depression (see WARNINGS and SPECIAL PRECAUTIONS), ataxia, falling, dizziness, headache. These occur predominantly at the start of therapy and most frequently in elderly patients, but may disappear with repeated administration.

Anterograde amnesia, which may be associated with inappropriate behaviour, has been reported.

Paradoxical reactions such as hallucinations, restlessness, agitation, nightmares, delusions, aggressiveness and psychoses may occur. In these cases NYXE should be discontinued.

The following side effects have been reported and frequencies are unknown:

Reduced alertness, fatigue, numbed emotions, asthenia, balance disorder. These occur predominantly at the start of therapy and most frequently in elderly patients, but may disappear with repeated administration.

Gastrointestinal disorders:

Less frequent: Nausea, diarrhoea, vomiting, dry mouth, abdominal or gastric pain, constipation, flatulence, frequent bowel movements, heartburn.

Musculoskeletal, connective tissue and bone disorders:

The following side effect has been reported and frequency is unknown: Muscle weakness, myalgia.

Eye disorders:

Less frequent: Diplopia, eye redness, blurred vision, visual depth perception altered.

Ear and labyrinth disorders:

Less frequent: Labyrinthitis, tinnitus, vertigo.

Reproductive system disorders:

Less frequent: Menorrhagia, vulvovaginal dryness.

Skin and subcutaneous tissue disorders:

Less frequent: Urticaria.

Renal and urinary disorders:

Less frequent: Dysuria.

General disorders and administrative site conditions:

Paraesthesia, hypotension.

Rebound effects: Abrupt withdrawal of NYXE even after short term use may result in a transient withdrawal syndrome of anxiety, restlessness, insomnia and mood changes, as well as an enhancement of symptoms that led to treatment with NYXE. (See WARNINGS and SPECIAL PRECAUTIONS). Taper dose. (See DIRECTIONS FOR USE).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms of overdose:

(See SIDE EFFECTS).

Overdose is usually manifested by varying degrees of central nervous system depression ranging from drowsiness to coma according to the quantity ingested. Individuals have recovered fully from NYXE doses of up to 400 mg. Overdose may be life-threatening especially when combined with other CNS depressants (including alcohol).

Treatment of overdose:

Treatment is symptomatic and supportive.

Activated charcoal may be given orally, especially in children who have ingested more than 5 mg.

Gastric lavage should be performed soon after ingestion and especially if more than 100 mg NYXE has been ingested. Sedatives should be withheld even if excitation occurs. NYXE is not dialyzable. Flumazenil may be useful in reversing sedative and respiratory depressant effects of NYXE but may contribute to the appearance of neurological symptoms (convulsions).

IDENTIFICATION

NYXE 5 mg: White to off – white, circular, biconvex, film – coated tablets, debossed with “E” on one side and “78” on the other side.

NYXE 10 mg: White to off – white, oval shaped, biconvex, film – coated tablets, debossed with “E” on one side and debossed with “80” with a score line between “8” and “0” on the other side.

PRESENTATION

NYXE 5 mg, NYXE 10 mg:

1. Blister Packs:

Tablets are packed in blister packs comprises of 250 µ clear PVC / PVdC film as the forming material and 25 µ Aluminium foil as the lidding material. Each blister contains 10 tablets.

Pack size: 30’s – Each carton contains 3 blisters of 10 tablets each.

2. HDPE Container Pack:

Tablets are packed in white opaque round 40 ml HDPE container with 33 mm neck finish closed with 33 mm 400 RS white opaque polypropylene ribbed stock closure with wad having induction sealing liner. The void space in the container is filled by Rayon coil 9 gm/yard.

Pack size: 30’s: One HDPE container of 30 tablets.

STORAGE INSTRUCTIONS

Store in a dry place at or below 25 °C. Protect from light.

Keep blisters in the original carton until required for use. Keep the HDPE container well closed.

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBER

NYXE 5 mg: 43/2.2/0258

NYXE 10 mg: 43/2.2/0248

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Novagen Pharma

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DATE OF PUBLICATION OF PACKAGE INSERT

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