Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nytamel 10 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains:
10 mg zolpidem tartrate.

Excipient(s) with known effect
Each film-coated tablet contains 85.88 mg lactose.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.

The tablet is white to off-white, oval, biconvex, film-coated, scored on both sides and debossedwith “ZIM” and “10” on one side. The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Zolpidem is indicated for short-term treatment of insomnia in adults in situations where the insomnia is debilitating or is causing severe distress for the patient.

4.2 Posology and method of administration

Treatment should be as short as possible. It should not exceed 4 weeks including the period of tapering off.

In certain cases extension beyond the maximum treatment period may be necessary; if so, extension beyond the maximum treatment period should not take place without re-evaluation of the patient's status, since the risk of abuse and dependence increases with the duration of treatment (see section 4.4).

Adults
The treatment should be taken in a single intake and not be re-administered during the same night.

The recommended daily dose for adults is 10 mg to be taken immediately at bedtime. The lowest effective daily dose of zolpidem should be used and must not exceed 10 mg.

Special populations

Elderly
In elderly or debilitated patients who may be especially sensitive to the effects of zolpidem a dose of 5 mg is recommended. This dose should only be increased to 10 mg where the clinical response is inadequate and the drug is well tolerated.

Mild to moderate hepatic impairment
As clearance and metabolism of zolpidem tartrate is reduced in hepatic impairment, dosage should begin at 5 mg in these patients.
This dose should only be increased to 10 mg where the clinical response is inadequate and the drug is well tolerated.
Use in severe hepatic impairment is contraindicated (see section 4.3).

Maximum dose
The total daily dose of zolpidem must not exceed 10 mg in any patient.

Paediatric population
Zolpidem is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. The available evidence from placebo-controlled clinical trials is presented in section 5.1.

Method of administration
For oral use.
The product should be taken with fluid just before going to bed.

4.3 Contraindications

Zolpidem tartrate is contraindicated in patients:

- with hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- with severe hepatic insufficiency
- with acute and/or severe respiratory insufficiency
- known to have previously experienced complex sleep behaviours after taking zolpidem, see section 4.4
- with sleep apnoea syndrome.
- with Myasthenia gravis.

4.4 Special warnings and precautions for use

Warnings

General information relating to effects seen following administration of benzodiazepines or other hypnotic agents which should be taken into account by the prescribing physician are described below.

Respiratory insufficiency
As hypnotics have the capacity to depress respiratory drive precautions should be observed if zolpidem is prescribed to patients with compromised respiratory function.

Duration of treatment
The duration of treatment should be as short as possible (see section 4.2), but should not exceed 4 weeks including the tapering off process. Extension beyond these periods should not take place without re-evaluation of the situation.
It may be useful to inform the patient when treatment is started that it will be of limited duration.

Risk from concomitant use of opioids
Concomitant use of zolpidem and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as zolpidem with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe zolpidem concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).
The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their environment to be aware of these symptoms (see section 4.5).

Hepatic insufficiency
Benzodiazepines and benzodiazepine-like agents are not indicated for the treatment of patients with severe hepatic insufficiency as they may precipitate encephalopathy.

Dependence
Use of zolpidem may lead to the development of abuse and/or physical and psychological dependence. The risk of dependence increases with dose and duration of treatment. The risk of abuse and dependence is also greater in patients with a history of psychiatric disorders and/or alcohol, substance or drug abuse. Zolpidem should be used with extreme caution in patients with current or a history of alcohol, substance or drug abuse or dependence. If physical dependence is developed, a sudden discontinuation of treatment will be accompanied by withdrawal symptoms. These may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

Precautions

The cause of insomnia should be identified wherever possible and the underlying factors treated before a hypnotic is prescribed. The failure of insomnia to remit after a 7-14 day course of treatment may indicate the presence of a primary psychiatric or physical disorder and the patient should be carefully re-evaluated at regular intervals.

Specific patient groups

Elderly or debilitated patients

should receive a lower dose: see recommended dosage (section 4.2).

Due to the myorelaxant effect, there is a risk of falls and consequent injury particularly for elderly patients when they get up at night.

Psychotic illnesses

Hypnotics such as zolpidem are not recommended for the primary treatment of psychoses.

Use in patients with a history of drug or alcohol abuse

Extreme caution should be exercised when prescribing for patients with a history of drug or alcohol abuse. These patients should be under careful surveillance when receiving zolpidem tartrate or any other hypnotic, since they are at risk of habituation and psychological dependence.

Next-day psychomotor impairment

Like other sedative/hypnotic drugs, zolpidem has CNS-depressant effects. The risk of next-day psychomotor impairment, including impaired driving ability, is increased if:

- zolpidem is taken within less than 8 hours before performing activities that require mental alertness (see section 4.7)
- a dose higher than the recommended dose is taken
- zolpidem is co-administered with other CNS depressants or with other drugs that increase the blood levels of zolpidem, or with alcohol or illicit drugs (see section 4.5).

Zolpidem should be taken in a single intake immediately at bedtime and not be re-administered during the same night.

Amnesia

Sedative/hypnotic agents such as zolpidem may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product. In order to reduce the risk, patients should ensure that they will be able to have an uninterrupted sleep of 8 hours (see section 4.8).

Depression and Suicidality

Some epidemiological studies show an increased incidence of completed suicide and suicide attempt in patients with or without depression, treated with hypnotics such as zolpidem. A causal relationship has not been established.

Although no clinically significant pharmacokinetic and pharmacodynamic interactions with SSRIs have been demonstrated (see section 4.5 Interactions with other medicinal products and other forms of interaction), as with other sedative/hypnotic drugs, zolpidem tartrate should be administered with caution in patients exhibiting symptoms of depression.

Suicidal tendencies may be present therefore the least amount of zolpidem that is feasible should be supplied to these patients to avoid the possibility of intentional overdosage by the patient. Pre-existing depression may be unmasked during use of zolpidem. Since insomnia may be a symptom of depression, the patient should be re-evaluated if insomnia persists.

Benzodiazepines and benzodiazepine-like agents should not be used alone to treat depression or anxiety associated with depression (suicide may be precipitated in such patients).

General information

Tolerance

Some loss of efficacy to the hypnotic effects of sedative/hypnotic agents like zolpidem may develop after repeated use for a few weeks.

Rebound insomnia

A transient syndrome whereby the symptoms that led to treatment with sedative/hypnotic agents recur in an enhanced form may occur on withdrawal of hypnotic treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness. Since the risk of withdrawal phenomena or rebound has been shown to be greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually where clinically appropriate. It is important that the patient should be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur when the medicinal product is discontinued. In the case of sedative/hypnotic agents with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high.

Severe Injuries

Due to its pharmacological properties, zolpidem can cause drowsiness and a decreased level of consciousness, which may lead to falls and consequently to severe injuries, see also section 4.8.

Patients with Long QT syndrome

An in vitro cardiac electrophysiological study showed that under experimental conditions using very high concentration and pluripotent stem cells zolpidem may reduce the hERG related potassium currents. The potential consequence in patients with congenital long QT syndrome is unknown. As a precaution, the benefit/risk ratio of zolpidem treatment in patients with known congenital long QT syndrome should be carefully considered.

Other Psychiatric and "paradoxical" reactions

Other Psychiatric and "paradoxical" reactions like restlessness, increased insomnia, agitation, irritability, aggression, delusion, rages, nightmares, hallucinations, psychoses, abnormal behaviour and other adverse behavioural effects are known to occur when using sedative/hypnotic agents like zolpidem. Should this occur, use of the product should be discontinued. These reactions are more likely to occur in the elderly.

Somnambulism and associated behaviours

Complex sleep behaviours, including sleep walking, and other associated behaviours such as "sleep driving", preparing and eating food, making phone calls or having sex, with amnesia for the event have been reported in patients who had taken zolpidem and were not fully awake. These events may occur following the first or any subsequent use of zolpidem. Discontinue treatment immediately if a patient experiences a complex sleep behaviour, due to the risk to the patient and others (see section 4.3). The use of alcohol and other CNS-depressants with zolpidem appears to increase the risk of such behaviours, as does the use of zolpidem at doses exceeding the maximum recommended dose.

Patients with renal insufficiency (see section 5.2)

Although dose adjustment is not necessary, caution should be exercised.

Excipients

NytamelThis medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

Alcohol
Concomitant intake with alcohol is not recommended. The sedative effect may be enhanced when the product is used in combination with alcohol. This affects the ability to drive or use machines.

Combination with CNS depressants
Caution should be exercised when Zolpidem is used in combination with other CNS depressants (see section 4.4). Enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, antiepileptic drugs, anaesthetics and sedative antihistamines. Therefore, concomitant use of zolpidem with these drugs may increase drowsiness and next-day psychomotor impairment, including impaired driving ability (see sections 4.4 and 4.7). Also, isolated cases of visual hallucinations were reported in patients taking zolpidem with antidepressants including bupropion, desipramine, fluoxetine, sertraline and venlafaxine.

Co-administration of fluvoxamine may increase blood levels of zolpidem, concurrent use is not recommended.

In the case of narcotic analgesics enhancement of euphoria may also occur leading to an increase in psychological dependence.

Opioids
The concomitant use of sedative medicines such as benzodiazepines or related drugs such as zolpidem with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4).

CYP450 inhibitors and inducers
Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of some hypnotics like zolpidem.

Zolpidem is metabolised via several hepatic cytochrome P450 enzymes, the main enzyme being CYP3A4 with the contribution of CYP1A2. The pharmacodynamic effect of zolpidem is decreased when it is administered with a CYP3A4 inducer such as rifampicin and St John's Wort. Co-administration of St. John's Wort may decrease blood levels of zolpidem, concurrent use is not recommended.

However, when zolpidem was administered with itraconazole (a CYP3A4 inhibitor) its pharmacokinetics and pharmacodynamics were not significantly modified. The clinical relevance of these results is unknown.

Co-administration of zolpidem with ketoconazole (200 mg twice daily), a potent CYP3A4 inhibitor, prolonged zolpidem elimination half-life, increased total AUC, and decreased apparent oral clearance when compared to zolpidem plus placebo. The total AUC for zolpidem was increased modestly, when co-administered with ketoconazole, it increased by a factor of 1.83

when compared to zolpidem alone. A routine dosage adjustment of zolpidem is not considered necessary, but patients should be advised that use of zolpidem with ketoconazole may enhance the sedative effects.

Co- administration ciprofloxacin may increase blood levels of zolpidem, concurrent use is not recommended.

Other drugs
When zolpidem was administered with warfarin, haloperidol, chlorpromazine, itraconazole, digoxin, ranitidine, no significant pharmacokinetic interactions were observed.

4.6 Fertility, pregnancy and lactation

Pregnancy
The use of zolpidem is not recommended during pregnancy.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Zolpidem crosses the placenta.

A large amount of data on pregnant women (more than 1,000 pregnancy outcomes) collected from cohort studies has not demonstrated evidence of the occurrence of malformations following exposure to benzodiazepines or benzodiazepine-like substances during the first trimester of pregnancy. However, certain case-control studies reported an increased incidence of cleft lip and palate associated with use of benzodiazepines during pregnancy.

Cases of reduced foetal movement and foetal heart rate variability have been described after administration of benzodiazepines or benzodiazepine-like substances during the second and/or third trimester of pregnancy. Administration of zolpidem during the late phase of pregnancy or during labour has been associated with effects on the neonate, such as hypothermia, hypotonia, feeding difficulties ('floppy infant syndrome'), and respiratory depression, due to the pharmacological action of the product. Cases of severe neonatal respiratory depression have been reported.

Moreover, infants born to mothers who took sedative/hypnotic agents chronically during the latter stages of pregnancy may have developed physical dependence and may be at risk of developing withdrawal symptoms in the postnatal period. Appropriate monitoring of the newborn in the postnatal period is recommended.

If Nytamel is prescribed to a woman of childbearing potential, she should be warned to contact her physician about stopping the product if she intends to become or suspects that she is pregnant.

Breast-feeding
Small quantities of zolpidem appear in breast milk. The use of zolpidem in nursing mothers is therefore, not recommended. The effect of zolpidem on newborns/infants is unknown.

4.7 Effects on ability to drive and use machines

Zolpidem has major influence on the ability to drive and use machines.

Vehicle drivers and machine operators should be warned that, as with other hypnotics, there may be a possible risk of drowsiness, prolonged reaction time, dizziness, sleepiness, blurred/double vision and reduced alertness and impaired driving the morning after therapy (see section 4.8). In order to minimise this risk a resting period of at least 8 hours is recommended between taking zolpidem and driving, using machinery and working at heights.
Driving ability impairment and behaviours such as 'sleep-driving' have occurred with zolpidem alone at therapeutic doses.

Furthermore, the co-administration of zolpidem with alcohol and other CNS depressants increases the risk of such behaviours (see section 4.4 and 4.5). Patients should be warned not to use alcohol or take other psychoactive substances when taking zolpidem.

4.8 Undesirable effects

In this section frequencies of undesirable effects are defined as follows:
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), very rare (< 1/10,000), not known (cannot be estimated from the available data).

There is evidence of a dose-relationship for adverse effects associated with zolpidem use, particularly for certain CNS events. As recommended in section 4.2, they should in theory, be less if zolpidem is taken immediately before retiring, or in bed. They occur most frequently in elderly patients.

Infections and infestations
Common: Upper respiratory tract infection, lower respiratory tract infection.

Immune system disorders
Not known: Angioedema.

Metabolism and nutrition disorders
Uncommon: Appetite disorder.

Psychiatric disorders
Common: Hallucination, agitation, nightmare, depression (see section 4.4).
Uncommon: Confusional state,irritability, restlessness, aggression, somnambulism (see section 4.4), euphoric mood, complex sleep behaviours (see section 4.4).
Rare: Libido disorder.
Very rare: Delusion, dependence, withdrawal symptoms, or rebound effects may occur after treatment discontinuation.
Not known: Anger, abnormal behaviour.
Most of these psychiatric undesirable effects are related to paradoxical reactions (see section 4.4).

Nervous system disorders
Common: Somnolence (also during the following day), reduced alertness,headache, dizziness, exacerbated insomnia, cognitive disorders such as memory disorders (memory impairment, amnesia, anterograde amnesia), ataxia.
Uncommon: Paraesthesia, tremor, disturbance in attention, speech disorder.
Rare: Depressed level of consciousness.

Eye disorders
Common: Diplopia, vision blurred.
Rare: Visual impairment.

Ear and labyrinth disorders
Common: Vertigo

Respiratory, thoracic and mediastinal disorders
Very rare: Respiratory depression (see section 4.4).

Gastrointestinal disorders
Common: Diarrhoea, nausea, vomiting, abdominal pain.

Hepatobiliary disorders
Uncommon: Liver enzymes elevated.
Rare: Hepatocellular, cholestatic or mixed liver injury (see section 4.2, 4.3 and 4.4).

Skin and subcutaneous tissue disorders
Uncommon: Rash, pruritus, hyperhidrosis.
Rare: Urticaria.

Musculoskeletal connective tissue and bone disorders
Common: Back pain.
Uncommon: Arthralgia, myalgia, muscle spasms, neck pain, muscular weakness.

General disorders and administration site conditions
Common: Fatigue.
Uncommon: Gait disturbance, fall (predominantly in elderly patients and when zolpidem was not taken in accordance with prescribing recommendation (see section 4.4).
Not known: Drug tolerance.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Signs & symptoms
In cases of overdose involving zolpidem alone, or with other CNS-depressant agents (including alcohol) impairment of consciousness up to coma, and more severe symptomatology, including fatal outcomes have been reported.

Individuals have fully recovered from overdoses up to 400 mg of zolpidem, 40 times the recommended dose.

Management
General symptomatic and supportive measures should be used. Immediate gastric lavage should be used where appropriate. Intravenous fluids should be administered as needed. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Monitoring of respiratory and cardiovascular functions should be considered. Sedating drugs should be withheld even if excitation occurs.

Use of flumazenil may be considered where serious symptoms are observed. However, flumazenil administration may contribute to the appearance of neurological symptoms (convulsions).

In the treatment of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken.

Due to the high distribution volume and protein binding of zolpidem, haemodialysis and forced diuresis are not effective measures. Haemodialysis studies in patients with renal failure receiving therapeutic doses have demonstrated that zolpidem is not dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hypnotics and Sedatives, Benzodiazepine related drugs
ATC Code: NO5C FO2

Zolpidem tartrate is an imidazopyridine which selectively binds the omega-1 receptor subtype (also known as the benzodiazepine-1 subtype) which is the alpha unit of the GABA-A receptor complex. Whereas benzodiazepines non-selectively bind all three omega receptor subtypes, zolpidem tartrate preferentially binds the omega-1 subtype. The clinical relevance is not known. The modulation of the chloride anion channel via this receptor leads to the specific sedative effects demonstrated by zolpidem tartrate. These effects are reversed by the benzodiazepine antagonist flumazenil.

In animals: The selective binding of zolpidem to omega-1 receptors may explain the virtual absence at hypnotic doses of myorelaxant and anti-convulsant effects in animals which are normally exhibited by benzodiazepines which are not selective for omega-1 sites.

In humans: The preservation of deep sleep (stages 3 and 4 - slow-wave sleep) may be explained by the selective omega-1 binding by zolpidem tartrate. All identified effects of zolpidem tartrate are reversed by the benzodiazepine antagonist flumazenil.

Preliminary single dose studies did not reveal respiratory depressant effects in normal subjects or in mild or moderate COPD.

Zolpidem tartrate acts rapidly and therefore should be taken immediately before retiring, or in bed.

The randomised trials only showed convincing evidence of efficacy of 10 mg zolpidem.
In a randomised double-blind trial in 462 non-elderly healthy volunteers with transient insomnia, zolpidem 10 mg decreased the mean time to fall asleep by 10 minutes compared to placebo, while for 5 mg zolpidem this was 3 minutes.

In a randomised double-blind trial in 114 non-elderly patients with chronic insomnia, zolpidem 10 mg decreased the mean time to fall asleep by 30 minutes compared to placebo, while for 5 mg zolpidem this was 15 minutes.
In some patients, a lower dose of 5 mg could be effective.

Paediatric population
Safety and efficacy of zolpidem have not been established in children aged less than 18 years. A randomized placebo-controlled study in 201 children aged 6-17 years with insomnia associated with Attention Deficit Hyperactivity Disorder (ADHD) failed to demonstrate efficacy of zolpidem 0.25 mg/kg/day (with a maximum of 10 mg/day) as compared to placebo. Psychiatric and nervous system disorders comprised the most frequent treatment emergent adverse events observed with zolpidem versus placebo and included dizziness (23.5 % versus 1.5 %), headache (12.5 % versus 9.2 %), and hallucinations (7.4 % versus 0 %) (see sections 4.2).

5.2 Pharmacokinetic properties

Absorption
Zolpidem tartrate has both a rapid absorption and onset of hypnotic action. Bioavailability is 70 % following oral administration and demonstrates linear kinetics in the therapeutic dose range. Peak plasma concentration is reached at between 0.5 and 3 hours.

Distribution
The distribution volume in adults is 0.54 l/kg ± 0.02 l/kg and decreases to 0.34 l/kg ± 0.05 l/kg in the very elderly.
Protein binding amounts to 92.5 % ± 0.1 %. First pass metabolism by the liver amounts to approximately 35 %. Repeated administration has been shown not to modify protein binding indicating a lack of competition between zolpidem and its metabolites for binding sites.

Elimination
The elimination half-life is short, with a mean of 2.4 hours (0.7-3.5) and a duration of action up to 6 hours.
All metabolites are pharmacologically inactive and are eliminated in the urine (56 %) and in the faeces (37 %).
Zolpidem has been shown in trials to be non-dialysable.

Special populations
Plasma concentrations in elderly subjects and those with hepatic impairment are increased. In patients with renal insufficiency, whether dialysed or not there is a moderate reduction in clearance. The other pharmacokinetic parameters are unaffected.

5.3 Preclinical safety data

No data of therapeutic relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Microcrystalline cellulose
Type A sodium starch glycolate
Magnesium stearate
Hypromellose.

Coating:
Hypromellose
Titanium dioxide (E171)
Macrogol 400.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

The film-coated tablets are packed in:

- PVC/PE/PVDC/Al blisters in carton boxes.
- HDPE tablet containers sealed with a child-proof PP closure.

Nytamel film-coated tablets are available in:

- cartons containing 4, 5, 7, 10, 14, 15, 20, 25, 28, 30, 40, 50, 60, 70, 80, 90, 100, 150 or 500 tablets packed in blisters.
- tablet containers containing 30, 100 or 500 tablets, sealed with a childproof closure.

Not all pack sizes may be marketed

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
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8 MARKETING AUTHORISATION NUMBER

PA0126/117/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 March 2002

Date of last renewal: 26 July 2006

10 DATE OF REVISION OF THE TEXT

June 2022