Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nytamel 5 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect
Each film-coated tablet contains 42.94 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, debossed with "ZIM" and "5" on one side.

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

Posology
Treatment should be as short as possible. Generally, the duration of treatment varies from a few days to two weeks with a maximum, including the tapering off process, of four weeks. The tapering off process should be tailored to the individual.

In certain cases, extension beyond the maximum treatment period may be necessary; if so, it should not take place without re-evaluation of the patient's status.

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 immediately at bedtime. The lowest effective daily dose of zolpidem should be used and must not exceed 10 mg.

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.

Hepatic impairment
Patients with hepatic insufficiency who do not clear the drug as rapidly as normal individuals, 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.

The total dose of zolpidem should 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

- Severe hepatic insufficiency.
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Sleep apnoea syndrome.
- Myasthenia gravis.
- Severe respiratory insufficiency.
- Children and adolescents under 18 years of age.

4.4 Special warnings and precautions for use

General
The cause of insomnia should be identified wherever possible. The underlying factors should be 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, which should be evaluated.
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.

Tolerance
Some loss of efficacy to the hypnotic effects of short-acting benzodiazepines and benzodiazepine-like agents may develop after repeated use for a few weeks.

Dependence
Use of benzodiazepines or benzodiazepine-like agents may lead to the development of physical and psychological dependence of these products. The risk of dependence increases with dose and duration of treatment and is also greater in patients with a history of psychiatric disorders and/or alcohol or drug abuse.
Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches or muscle pain, extreme anxiety and 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.

Rebound insomnia
A transient syndrome whereby the symptoms that led to treatment with a benzodiazepines or benzodiazepine-like agent recur in an enhanced form, may occur on withdrawal of hypnotic agent. It may be accompanied by other reactions including mood changes, anxiety and restlessness.
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 being discontinued.
There are indications that, in the case of benzodiazepines and benzodiazepine-like agents with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high.
As the risk of withdrawal symptoms/rebound phenomena are more likely to develop after abrupt discontinuation of treatment, it is recommended to decrease the dose gradually.

Next-day psychomotor impairment
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.

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.

Amnesia

Benzodiazepines or benzodiazepine-like agents may induce anterograde amnesia. The condition usually occurs 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).

Psychiatric and "paradoxical" reactions

When using benzodiazepines or benzodiazepine-like agents, reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, somnambulism, inappropriate behaviour, increased insomnia and other adverse behavioural effects are known to occur. Should this occur, use of the product should be discontinued. These reactions are more likely to occur in the elderly.

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 caregivers (where applicable) to be aware of these symptoms (see section 4.5).

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 consequently of hip fractures particularly for elderly patients when they get up at night.

Patients with renal insufficiency (see section 5.2)

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

Patients with chronic respiratory insufficiency

Caution should be observed when prescribing zolpidem since benzodiazepines have been shown to impair respiratory drive. It should also be taken into consideration that anxiety or agitation have been described as signs of decompensated respiratory insufficiency.

Patients with severe hepatic insufficiency

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

Use in patients with psychotic illness:

Benzodiazepines and benzodiazepine-like agents are not recommended for the primary treatment.

Use in depression: Despite the fact that relevant clinical, pharmacokinetic and pharmacodynamic interactions with SSRI have not been demonstrated, zolpidem should be administered with caution in patients exhibiting symptoms of depression. Suicidal

tendencies may be present. Due to the possibility of intentional overdose by the patient, the lowest amount of drug that is feasible should be supplied to these patients.

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).

Use in patients with a history of drug or alcohol abuse: Benzodiazepines and benzodiazepine-like agents should be used with extreme caution in patients with a history of alcohol or drug abuse. These patients should be under careful surveillance when receiving zolpidem since they are at risk of habituation and psychological dependence.

Excipients

This 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

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 (see sections 4.8 and 5.1). Therefore, concomitant use of zolpidem with these drugs may increase drowsiness and next-day psychomotor impairment, including impaired driving ability (see section 4.4 and section 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
Zolpidem is metabolised by some enzymes of the cytochrome P450-family. The main enzyme is CYP3A4.
Rifampicin induces the metabolism of zolpidem, resulting in approximately 60 % reduction in peak plasma concentrations and possibly decreased efficacy. Similar effects might be expected also with other strong inducers of cytochrome P450-enzymes.

Compounds that inhibit hepatic enzymes (particularly CYP3A4) may increase plasma concentrations and enhance the activity of zolpidem. However, when zolpidem is administrated with itraconazole (CYP3A4 inhibitor), the pharmacokinetic and pharmacodynamic effects are not significantly different. The clinical relevance of these results is unknown.

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

4.6 Fertility, pregnancy and lactation

There are insufficient data to permit an assessment of the safety of zolpidem during pregnancy and lactation.

Pregnancy
Although animal studies have shown no teratogenic or embryotoxic effects, safety in pregnancy has not been established in humans. Therefore, zolpidem should not be used during pregnancy especially in the first trimester.

If the product is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuance of the product if she intends to become or suspect that she is pregnant.

If, for compelling medical reason, zolpidem is administered during the late phase of pregnancy, or during labour, effects on the neonate, such as hypothermia, hypotonia and moderate respiratory depression, can be expected due to the pharmacological action of the product.

Infants born to mothers who took benzodiazepines or benzodiazepine-like agents chronically during the latter stages of pregnancy may develop withdrawal symptoms in the postnatal period as a result of physical dependence.

Breast-feeding
Zolpidem passes into breast milk in minimal amounts. Zolpidem should therefore not be used during breast-feeding since effects on the infant are not studied.

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 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).
These effects seem to be related with individual sensitivity and to appear more often within the hour following the drug intake if the patient does not go to bed or does not sleep immediately (see section 4.2).

Psychiatric disorders
Uncommon: Paradoxical reactions: Restlessness, agitation, irritability, aggressiveness, delusions, rage, nightmares, hallucinations, psychoses, somnambulism, inappropriate behaviour and other adverse behavioural effects (such reactions are more likely to occur in the elderly, see section 4.4), anterograde amnesia, which may be associated with inappropriate behaviour.

Pre-existing depression may become manifest during use of benzodiazepines or benzodiazepine-like agents (see section 4.4).
Use (even at therapeutic dosages) may lead to physical dependence: Discontinuation of the therapy may result in withdrawal or rebound phenomena (see section 4.4).
Psychological dependence may occur. Abuse has been reported in polydrug abusers.
Decreased libido.

Nervous system disorders
Common: Drowsiness during the following day, numbed emotions, reduced alertness, confusion, fatigue, headache

Eye disorders
Common: Double vision

Ear and labyrinth disorders
Common: Vertigo, ataxia

Gastrointestinal disorders
Uncommon: Gastrointestinal disturbances (diarrhoea, nausea, vomiting)

Skin and subcutaneous tissue disorders
Uncommon: Skin reactions

Musculoskeletal connective tissue and bone disorders
Common: Muscle weakness

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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms
In reports of overdose with zolpidem alone, impairment of consciousness has ranged from somnolence to light coma. 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 when serious symptoms are observed. 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, an imidazopyridine is a benzodiazepine-like hypnotic agent. In experimental studies it was shown that it has sedative effects at lower dosages than those required to exert anticonvulsant, myorelaxant or anxiolytic effects. These effects are related to a specific agonist action at central receptors belonging to the" GABA-omega" (BZ1 & BZ2) macromolecular receptor" complex, modulating the opening of the chloride ion channel. Zolpidem acts primarily upon omega (BZ1) receptor subtypes. The clinical relevance of this is not known.

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 and 4.3).

5.2 Pharmacokinetic properties

Absorption
Zolpidem has both a rapid absorption and onset of hypnotic effect. Bioavailability is 70% following oral administration. It demonstrates linear kinetics in the therapeutic dose range. The therapeutic plasma level is between 80 and 200 ng/ml. Peak plasma concentration is reached at between 0.5 and 3 hours after administration.

Distribution
The distribution volume in adults is 0.54 L/kg and decreases to 0.34 L/kg in the elderly.
Protein binding amounts to 92%. 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 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
In patients with renal insufficiency, a moderate reduction in clearance is observed (independent of possible dialysis). The other pharmacokinetic parameters remain unaffected.

In elderly patients and in patients with hepatic insufficiency, the bio-availability of zolpidem is increased. Clearance is reduced and the elimination half-life is prolonged (approximately 10 hours).

In patients with liver cirrhosis a 5-fold increase in AUC and a 3-fold increase in half-life was observed.

5.3 Preclinical safety data

Preclinical effects were only observed at dosages well above the maximum human exposure levels and are therefore of little significance for clinical use.

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.

6.6 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
Waterford Road
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8 MARKETING AUTHORISATION NUMBER

PA0126/117/001

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

May 2020