SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zopiclone 7.5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Zopiclone 7.5mg contains 7.5 mg of Zopiclone per tablet.

Excipient(s) with known effect
Each tablet contains 31.37 mg lactose (as lactose monohydrate).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.
White, odourless, round, convex film-coated tablets with embossing “ZOC 7.5” with score line on one side and snap tab on the other side. Diameter approximately 7.0 mm.
The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1. Therapeutic indications

Zopiclone is indicated for the treatment of insomnia in adults

4.2 Posology and method of administration

Posology
Treatment with Zopiclone should be for as short a period as possible. Long-term continuous use is not recommended (see section 4.4).

The period of treatment should generally vary between a few days to 2 weeks, with a maximum of 4 weeks including the tapering off phase. It is recommended that the patient should be informed of this prior to commencing treatment. In certain cases it may be necessary to prolong treatment to beyond the maximum period. If this is the case, however, it should only take place after re-evaluation of the patient’s condition.

The usual dose of Zopiclone in healthy adults is 7.5 mg, taken by oral administration in an upright position 30 to 60 minutes before retiring.

Paediatric population
Zopiclone should not be used in children and adolescents less than 18 years. The safety and efficacy of zopiclone in children and adolescents aged less than 18 years have not been established.

Patients with hepatic insufficiency
As elimination of zopiclone may be reduced in patients with hepatic dysfunction, a lower dose of 3.75mg zopiclone nightly is recommended. The standard dose of 7.5mg zopiclone may be used with caution in some cases, depending on effectiveness and acceptability.

Renal insufficiency
Accumulation of zopiclone or its metabolites has not been seen during treatment of insomnia in patients with renal insufficiency. However, it is recommended that patients with impaired renal function should start treatment with 3.75mg.

Chronic respiratory insufficiency
In patients with chronic respiratory insufficiency, a starting dose of 3.75 mg zopiclone is recommended initially. The dosage subsequently may be increased to 7.5 mg.

Special populations
In the elderly, patients with hepatic insufficiency or chronic respiratory insufficiency, treatment should be started at a dosage of 3.75 mg (see section 4.4).

Method of administration
Oral. Each film coated tablet should be swallowed whole without sucking, chewing or breaking.

Treatment should be started with the lowest recommended dose. A total daily dose of 7.5 mg should not be exceeded.

4.3 Contraindications

Zopiclone tablets are contraindicated in the following cases:

- myasthenia gravis
- severe respiratory insufficiency
- sleep apnoea syndrome
- severe hepatic insufficiency
- hypersensitivity to zopiclone or to any of the excipients, benzodiazepines or other benzodiazepine-like substances
- children and adolescents under the age of 18 years (see section 4.2).

4.4 Special warnings and precautions for use

Before starting treatment with zopiclone any underlying cause of insomnia should be addressed carefully.

Dependence:

Clinical experience to date with Zopiclone suggests that the risk of dependence is minimal when the duration of treatment is limited to not more than 4 weeks.

The use of benzodiazepines and benzodiazepine-like substances can lead to the development of physical and psychological dependence on these agents. This may occur not only with misuse of high doses but also with therapeutical doses. The risk of dependence increases the higher the dose and the longer the period of treatment; the risk of dependence is also greater in patients with a history of alcohol or drug abuse or those who have marked personality disorder. The decision to use a hypnotic in such patients should be taken only with this clearly in mind. These patients should be under careful surveillance when receiving zopiclone.

If physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms (see warnings and precautions). These may be expressed as headaches, muscle pain, extreme anxiety, tension, restlessness, confusion, insomnia and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise or physical contact, hallucinations or epileptic seizures. Rare cases of abuse have been reported. (see section 4.8).

The termination of treatment with Zopiclone is unlikely to be associated with withdrawal effects when duration of treatment is limited to 4 weeks. Patients may benefit from tapering of the dose before discontinuation. (See also section 4.8. Undesirable Effects).

Depression:

As with other hypnotics, zopiclone does not constitute a treatment for depression. Benzodiazepines and benzodiazepine like substances should not be used as the sole treatment for depression or anxiety linked with depression (suicide may be triggered in such patients).

Any underlying cause on the insomnia should also be addressed before symptomatic treatment to avoid under treating potentially serious effects of depression.

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Pre-existing depression may be unmasked during use of zopiclone. Since insomnia may be a symptom of depression, the patient should be re-evaluated if insomnia persists

Rebound insomnia:

After discontinuation of treatment with a benzodiazepine or benzodiazepine-like agent recur in an enhanced form on discontinuation of therapy. It may be accompanied by other reactions including mood changes, sleep disturbances,

anxiety and restlessness. Since the risk of withdrawal symptoms or rebound symptoms is greater after prolonged treatment, or abrupt interruption of the treatment it is advisable to reduce the dosage gradually.

Period of treatment:
The period of treatment should employ the lowest effective dose and should be as short as possible (see section 4.2) and not longer than 4 weeks including the tapering off process. This period should only be exceeded after re-evaluation of the patient's condition. It may be of benefit to inform the patient at the beginning of treatment that the treatment will be of short duration, and to explain precisely how the dose will be gradually reduced. It is also important to point out to the patient the possibility of the occurrence of rebound phenomena in order to keep to a minimum any worries about the occurrence of such symptoms during the tapering off period of the treatment. In the case of benzodiazepines and benzodiazepine-like substances with a short period of action, there are indications that withdrawal symptoms may occur within the dosage interval, especially if the dose is high.

Tolerance:
The hypnotic effect of short-acting benzodiazepines and benzodiazepine-like substances may diminish after repeated use for a few weeks. For zopiclone however, no pronounced tolerance has occurred during a treatment period of up to 4 weeks.

Anterograde Amnesia:
Benzodiazepines and benzodiazepine-like substances may cause anterograde amnesia, especially when sleep is interrupted or when retiring to bed is delayed after taking the tablet. In order to reduce the risk patients should ensure that they will be able to have an uninterrupted sleep of 7-8 hours (see section 4.8).

Psychiatric and paradoxical reactions:
It is known that reactions such as restlessness, agitation, irritability, aggression, delusions, outbursts of rage, nightmares, hallucination, psychoses, inappropriate behaviour and other behavioural disturbances may occur during the use of benzodiazepines and benzodiazepine-like substances. If this is the case administration of the medicinal product should be discontinued. The risk of these reactions is greater in children and the elderly. Other psychiatric and paradoxical reactions have been reported (see Section 4.8).

Benzodiazepines and benzodiazepine-like substances are not recommended as the primary treatment of psychoses.

Somnambulism and associated behaviours:
Sleep walking and other associated behaviours such as "sleep driving", preparing and eating food, or making phone calls, with amnesia for the event, have been reported in patients who have taken zopiclone and were not fully awake. The use of alcohol and other CNS-depressants with zopiclone appears to increase the risk of such behaviours, as does the use of zopiclone at doses exceeding the maximum recommended dose. Discontinuation of zopiclone

should be strongly considered for patients who report such behaviours (see Section 4.5 Interactions with other medicinal products and other forms of interactions).

Specific patient groups
For the elderly:
Because of the myorelaxant effect of zopiclone there is a danger of falling over, particularly for elderly patients when they get up at night (see section 4.2).

Paediatric population
Zopiclone should not be used in children and adolescents less than 18 years.
The safety and efficacy of zopiclone in children and adolescents aged less than 18 years have not been established.

Chronic respiratory insufficiency
Precautions should be observed if zopiclone is prescribed to patients with compromised respiratory function (See section 4.8). A lower dose is advised for patients with chronic respiratory insufficiency due to the risk of masking the symptoms (anxiety, agitation) of respiratory depression, especially at night. Administration of Zopiclone in these patients should be considered carefully and a daily dose of 7.5 mg should not be exceeded (see section 4.2).

Severe hepatic insufficiency
Benzodiazepines and benzodiazepine-like substances are not suitable for the treatment of these patients since they may precipitate encephalopathy.

Patients with hepatic insufficiency or reduced renal function.
A reduced dosage is recommended (see section 4.2).

Patients with a history of alcohol or drug abuse
Benzodiazepines and benzodiazepine-like substances should be administered with extreme caution to these patients.

<u>Risk from concomitant use of opioids</u>
Concomitant use of zopiclone 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 zopiclone with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe zopiclone 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).

Driving: It has been reported that the risk that zopiclone adversely affects driving ability is increased by the concomitant intake of alcohol. Therefore, it

is recommended not to drive while taking zopiclone and alcohol concomitantly.

Excipients:
This product contains lactose; patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol
The sedative effect of zopiclone may be enhanced when used in combination with alcohol, concomitant use is therefore not recommended. In particular this could affect the patient's ability to drive or use machines.

Other medicinal products
In combination with CNS depressants an enhancement of the central depressive effect may occur. The therapeutic benefit of co-administration with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anti-epileptic drugs, anaesthetics and sedative antihistamines should therefore be carefully considered. Concomitant use of benzodiazepines or benzodiazepine-like agents with narcotic analgesics may enhance their euphoric effect and could lead to increased psychological dependence.

Compounds which inhibit or induce certain hepatic enzymes (particularly cytochrome P450) may enhance or reduce the activity of benzodiazepines and benzodiazepine-like agents.

Combination of zopiclone with muscle relaxants may increase the muscle relaxing effect.

The effect of erythromycin on the pharmacokinetics of zopiclone has been studied in 10 healthy subjects. The AUC of zopiclone is increased by 80% in presence of erythromycin which indicates that erythromycin can inhibit the metabolism of drugs metabolised by CYP 3A4. As a consequence, the hypnotic effect of zopiclone may be enhanced.

Since zopiclone is mainly metabolised by CYP 3A4, plasma levels of zopiclone and thus the effects of zopiclone may be increased when used in combination with drugs which inhibit CYP 3A4, such as macrolide antibiotics, azole antimycotics and HIV protease inhibitors, as well as grapefruit juice, erythromycin, clarithromycin, ketoconazole, itraconazole and ritonavir. A dose reduction for zopiclone may be required when it is co-administered with CYP3A4 inhibitors.

Drugs which induce CYP 3A4, like phenobarbital, phenytoin, carbamazepine, rifampicin and products containing St John's wort, may reduce zopiclone plasma levels and thus the effect of zopiclone.

A single dose study has indicated that when zopiclone and carbamazepine are taken in combination, their sedative effects are additive. However, as carbamazepine is a potent inducer of CYP3A4, it is predicted that long term use of carbamazepine could result in a reduction of zopiclone plasma levels and reduce its hypnotic effects accordingly.

Opioids:
The concomitant use of sedative medicines such as benzodiazepines or related drugs such as zopiclone 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).

4.6 Fertility, pregnancy and lactation

Insufficient data are available on zopiclone to assess its safety during human pregnancy and lactation

Pregnancy:
Experience of use of zopiclone during pregnancy in humans is limited and the safety of use in pregnant women has not been established. To date, zopiclone has not produced injurious effects in animal studies except at very high maternally toxic doses. Use in pregnancy is therefore not recommended. If the product is prescribed to a woman of child bearing potential, she should be advised to contact her physician about stopping the product if she intends to become pregnant, or suspects that she is pregnant.

Moreover, if zopiclone is used during the last three months of pregnancy or during labour, due to the pharmacological action of the product, effects on the neonate, such as hypothermia, hypotonia, moderate respiratory depression, decreased muscle tone and suckling reflex ("floppy infant syndrome") can be expected.

Infants born to mothers who took benzodiazepines or benzodiazepine-like agents chronically during the latter stages of pregnancy may have developed physical dependence and may be at some risk of developing withdrawal symptoms in the postnatal period.

Breastfeeding:
The safety of use during lactation has not been established. Zopiclone is excreted in breast milk in very low concentrations, and use in nursing mothers must be avoided.

4.7 Effects on ability to drive and use machines

Sedation, amnesia, impaired concentration and impaired muscular function may reduce the capability to drive or operate machines. The risk is increased with concomitant alcohol intake. The risk is even higher when sleep duration is insufficient. Due to its effects Zopiclone may affect the ability to drive and use machines during the first hours after administration.

After normal use the residual effects the next morning are small, especially when dosages of 3.75 mg are taken. Patients should be warned not to drive or operate machines until treatment has finished or it has been established that their performance is unimpaired.

Use of zopiclone with alcohol may enhance the sedative effect and affect the patient's ability to drive and use machinery the following morning.

4.8 Undesirable effects

List of adverse reactions

The frequencies of adverse events are ranked according to the following: 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).

Undesirable effects seem to be related to individual sensitivity and to appear more often during the first hour following intake. The following adverse reactions have been observed in patients treated with zopiclone:

MedDRA system organ class	**Very common**	**Common**	**Rare**	**Very rare**	**Not known**
Immune system disorders				Anaphylactic reactions	
Psychiatric disorders			Numbed emotions, confusion and depression[2]. Paradoxical reactions[2], such as restlessness, agitation, irritability, aggression, delusions, outburst of rage, nightmares, hallucinations, psychoses, inappropriate	Decreased libido	Physical and psychological dependence[2]

MedDRA system organ class	Very common	Common	Rare	Very rare	Not known
			behaviour and other behavioural disturbances and somnambulism (see section 4.4).		
Nervous system disorders	Bitter taste or metallic after-taste	Sleepiness during the following day, reduced alertness, headache, dizziness	Amnesia[1], incordination, ataxia[3](predominantly at the beginning of treatment; generally disappears after repeated administration), light- headness		
Eye disorders			Double vision[3]		
Gastrointestinal disorders		Gastro-intestinal problems including nausea and vomiting	Dry mouth Dyspepsia		
Skin and subcutaneous disorders			Skin reactions including urticaria	Angioedema, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome	
Musculoskeletal, connective tissue and bone disorders			Muscle weakness		
General disorders and administration site conditions			Tiredness		

MedDRA system organ class	Very common	Common	Rare	Very rare	Not known
Investigations			Slight to moderate increases of serum transminases and/or alkaline phosphatase		
Injury, poisoning and procedural complications			Fall (predominantly in older people)		
Respiratory, thoracic and mediastinal disorders			dyspnoea (see section 4.4)		respiratory depression (see section 4.4)

[1] Amnesia

Anterograde amnesia may occur on therapeutic doses, and the risk is increased the higher the dose. This undesirable effect has been observed rarely. Amnesia may be accompanied by inappropriate behaviour (see section 4.4).

[2] Depression

Pre-existent depression may become manifest during the use of benzodiazepines and benzodiazepine-like substances (see section 4.4)

Psychiatric and paradoxical reactions

Reactions such as restlessness, agitation, irritability, aggression, delusions, outbursts of rage, nightmares, hallucinations, psychoses, inappropriate behaviour and other behavioural disturbances may occur during the use of benzodiazepines and benzodiazepine-like substances. In rare cases they may become quite severe with this agent. The risk of these reactions is greater in children and the elderly (see section 4.4).

Dependence

Use may lead to physical dependence even at therapeutic dosages: discontinuation of the treatment may lead to withdrawal or rebound phenomena (see section 4.4). Psychological dependence may also occur. Misuse has been reported.

[3] Predominantly at the beginning of treatment; generally disappears after repeated administration

Withdrawal syndrome

Withdrawal syndrome has been reported upon discontinuation of zopiclone. (See section 4.4). Withdrawal symptoms vary and may include rebound insomnia, anxiety, tremor, sweating, agitation, confusion, headache,

palpitations, tachycardia, delirium, nightmares, hallucinations, panic attacks, muscle aches/cramps, gastrointestinal disturbances and irritability. In very rare cases, seizures may occur.

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Fatal dose not known.

Symptoms

In the cases of overdosage reported, the reports were not accompanied by life-threatening effects unless the agent was ingested in combination with other drugs which have a suppressive effect on the central nervous system, including alcohol. In mild cases, symptoms include drowsiness, mental confusion, and lethargy. In more serious cases, symptoms may include ataxia, hypotonia, hypotension, methaemoglobinaemia, respiratory depression, rarely coma and very rarely death. Overdose of benzodiazepines or benzodiazepine-like agents is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma, depending on the amount ingested. Rarely, A-V block has occurred. Other risk factors, such as the presence of concomitant illness and the debilitated state of the patient, may contribute to the severity of symptoms and very rarely can result in fatal outcome.

Treatment

Consider activated charcoal if an adult has ingested more than 150 mg or a child more than 1.5 mg/kg within 1 hour. Alternatively consider gastric lavage in adults within 1 hour of a potentially life-threatening overdose. If CNS depression is severe consider the use of Flumazenil. It has a short shelf-life (about an hour). NOT TO BE USED IN MIXED OVERDOSE OR AS A ‘DIAGNOSTIC’ TEST. Management should include general symptomatic and supportive measures including a clear airway and monitoring cardiac and vital signs until stable.

Treatment should be aimed at supporting vital functions and is chiefly symptomatic (e.g. monitor the heart function and respiration). Gastric lavage or activated charcoal is only useful shortly after ingestion.

Haemodialysis is not useful because of the high distribution volume of zopiclone. Flumazenil may be beneficial as an antidote.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: benzodiazepine related drugs, ATC code: N05CF01

Zopiclone is a cyclopyrrolone which possesses similar sedative, anxiolytic, muscle relaxant and anticonvulsant properties as the benzodiazepines. Zopiclone recognizes specifically and with high affinity the central receptors of the $GABA_A$-benzodiazepine chloride channel macromolecular receptor complex in the central nervous system. After binding of Zopiclone to this receptor complex (at a site distinct from, but closely related to the benzodiazepine binding site), the affinity of the receptor complex for GABA increases. Binding of GABA to the complex induces opening of the chloride channels, through which hyperpolarisation of the cell membrane and inhibition of the neurons takes place.

Zopiclone has no affinity for peripheral benzodiazepine receptors.

Significant improvements in sleep onset time, sleep quality, number of awakenings and total sleep time were observed after administration of a single Zopiclone dose. The influence of Zopiclone on sleep architecture is minimal.

5.2 Pharmacokinetic properties

Zopiclone is rapidly absorbed following oral administration. The oral administration of 7.5 mg Zopiclone resulted in mean peak plasma concentrations of 54 to 86 µg/L at 0.5 to 2.5 hours after administration, yet the hypnotic effect enters already after 15 to 30 minutes. Zopiclone demonstrates linear pharmacokinetics between dosages of 3.5 to 15 mg.

After absorption Zopiclone is widely distributed into body tissues including the brain, with relative high concentrations in the liver and the left hypochondrium. The volume of distribution is about 100 L.

Zopiclone is reported to be bound to plasma proteins at a percentage of 45 to 80 %.

The renal clearance of unchanged Zopiclone is about 10 mL/min, the plasma clearance reaches values up to 230 mL/min.

Zopiclone has an elimination half-life of 3.5 to 6.5 hours. Because of this short elimination half-life there is no accumulation of Zopiclone in the body after repeated administration. In patients with renal and/or hepatic insufficiency and in elderly the elimination half-life of Zopiclone can be prolonged.

Zopiclone is extensively metabolised in the liver by three major pathways: Oxidation of the side chain resulting in the formation of the less active metabolite Zopiclone N-oxide (11 %), demethylation leading to the inactive metabolite N-desmethyl Zopiclone (15 %) and ester hydrolysis involving oxidative decarboxylation of 50 % of a dose, producing inactive metabolites partly eliminated via the lung as carbon dioxide. Only 4 to 5 % of the dose is excreted unchanged in the urine. About 16 % of the dose is excreted in faeces.

5.3 Preclinical safety data

Carcinogenicity: From studies performed in rats and mice it can be concluded that for patients receiving long-term medication with Zopiclone no carcinogenic potential exists.

Mutagenicity: Both *in vitro* and *in vivo* studies failed to show mutagenicity produced by Zopiclone.

Fertility: In animal studies Zopiclone caused a decrease in fertility in rats. Zopiclone did not affect fertility in rabbits.

Teratogenicity: Zopiclone did not show any teratogenic or embryotoxic effect in animal studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Calcium hydrogenphosphate
Maize starch
Pregelatinised starch
Sodium carboxymethyl cellulose
Colloidal anhydrous silica
Magnesium stearate
Titanium dioxide (E171)
Hypromellose.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original container.

6.5 Nature and contents of container

Lithographed carton boxes containing 1, 3 or 6 PVC/PVDC/aluminium strips of 10 tablets, and lithographed carton boxes containing 1, 2 or 4 PVC/PVDC/aluminium strips of 14 tablets. Each box contains a patient insert.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Ratiopharm GmbH
Graf-Arco-Strasse 3
D89070 Ulm
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 15773/0029

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