ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zerene 5 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 5 mg of zaleplon.

Excipient: Lactose monohydrate 54 mg.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard.
Capsules have an opaque white and opaque light brown hard shell with gold band, "W" and the strength "5 mg".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zerene is indicated for the treatment of patients with insomnia who have difficulty falling asleep. It is indicated only when the disorder is severe, disabling or subjecting the individual to extreme distress.

4.2 Posology and method of administration

For adults, the recommended dose is 10 mg.

Treatment should be as short as possible with a maximum duration of two weeks**.**

Zerene can be taken immediately before going to bed or after the patient has gone to bed and is experiencing difficulty falling asleep. As administration after food delays the time to maximal plasma concentration by approximately 2 hours no food should be eaten with or shortly before intake of Zerene.

The total daily dose of Zerene should not exceed 10 mg in any patient. Patients should be advised not to take a second dose within a single night.

Elderly
Elderly patients may be sensitive to the effects of hypnotics; therefore, 5 mg is the recommended dose of Zerene.

Paediatric patients
Zerene is contraindicated in children (see section 4.3).

Hepatic impairment
As clearance is reduced, patients with mild to moderate hepatic impairment should be treated with Zerene 5 mg. For severe hepatic impairment see section 4.3.

Renal impairment
No dosage adjustment is required in patients with mild to moderate renal insufficiency, because Zerene pharmacokinetics is not altered in such patients. Severe renal impairment is contraindicated (see section 4.3.).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients
Severe hepatic impairment
Severe renal impairment
Sleep apnoea syndrome
Myasthenia gravis
Severe respiratory insufficiency
Children (under 18 years of age)

4.4 Special warnings and precautions for use

Complex behaviours such as "sleep-driving" (i.e., driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) have been reported in patients taking sedative-hypnotics. These events can occur in sedative-hypnotic-naive as well as in sedative-hypnotic experienced persons. Although behaviours such as sleep-driving may occur with a sedative-hypnotic alone at therapeutic doses, the use of alcohol and other central nervous system (CNS) depressants with sedative-hypnotics appears to increase the risk of such behaviours, as does exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of zaleplon is recommended for patients who report a "sleep-driving" episode. Other complex behaviours (e.g., preparing and eating food, making phone calls, or having sex) have been reported in patients who are not fully awake after taking a sedative-hypnotic. As with sleep-driving, patients usually do not remember these events.

Severe anaphylactic/anaphylactoid reactions have been reported with the use of sedative-hypnotics, including zaleplon. Cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including zaleplon. Some patients taking sedative-hypnotics have had additional symptoms such as dyspnoea, throat closing, or nausea and vomiting. Some patients have required medical therapy in the emergency department. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with zaleplon should not be rechallenged with the active substance.

Insomnia may represent an underlying physical or psychiatric disorder. Insomnia that persists or worsens after a short course of zaleplon treatment may indicate a need to re-evaluate the patient.

Due to zaleplon's short plasma half-life, alternative therapy should be considered if early morning awakening is experienced. Patients should be advised not to take a second dose within a single night.

Co-administration of Zerene with medicinal products known to influence CYP3A4 is expected to result in changes in zaleplon's plasma concentrations. (See section 4.5)

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 and benzodiazepine-like agents may lead to physical and psychic dependence. The risk of dependence increases with dose and duration of treatment and is greater with patients having a history of alcohol and medicinal product abuse. Once physical dependence has developed, abrupt termination 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: unreality, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures. There have been post-marketing reports of dependence associated with zaleplon, predominantly in combination with other psychotropic agents.

Rebound insomnia and anxiety
A transient syndrome whereby the symptoms that led to the treatment with a benzodiazepine or benzodiazepine-like agent recur in an enhanced form, may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety, or sleep disturbances and restlessness.

Duration of treatment
The duration of treatment should be as short as possible (see section 4.2), and should not exceed two weeks. Extension beyond these periods should not take place without clinical re-evaluation of the patient.

It may be useful to inform the patient when treatment is started that it will be of limited duration. It is important that patients be aware of the possibility of rebound phenomena, thereby minimising anxiety should such symptoms develop when the medicinal product is discontinued.

Memory and psychomotor impairment
Benzodiazepines and benzodiazepine-like agents may induce anterograde amnesia and psychomotor impairment. These occur most often up to several hours after ingesting the product. To reduce the risk, patients should not undertake activities requiring psychomotor co-ordination until 4 hours or more after taking Zerene (see section 4.7).

Psychiatric and "paradoxical" reactions
Reactions like restlessness, agitation, irritability, decreased inhibition, aggressiveness, abnormal thinking, delusion, rages, nightmares, depersonalisation, hallucinations, psychoses, inappropriate behaviour, extroversion that seems out of character and other behavioural effects are known to occur when using benzodiazepines or benzodiazepine-like agents. They may be active substance-induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. These reactions are more likely to occur in the elderly. Should this occur, use of this product should be discontinued. Any new behavioural sign or symptom requires careful and immediate evaluation.

Specific patient groups

Alcohol and medicinal product abuse
Benzodiazepine and benzodiazepine-like agents should be used with extreme caution in patients with a history of alcohol or medicinal product abuse.

Hepatic impairment
Benzodiazepine and benzodiazepine-like agents are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy (see section 4.2). In patients with mild to moderate hepatic insufficiency, the bioavailability of zaleplon is increased because of reduced clearance, and the dose will therefore need to be modified in these patients.

Renal impairment
Zerene is not indicated to treat patients with severe renal impairment as it has not been adequately studied in those patients. In patients with mild to moderate renal impairment, the pharmacokinetic profile of zaleplon is not significantly different than that in healthy subjects. Hence, no dose adjustment is required in these patients.

Respiratory insufficiency
Caution should be observed when prescribing sedative medicinal products to patients with chronic respiratory insufficiency.

Psychosis
Benzodiazepine and benzodiazepine-like agents are not recommended for the primary treatment of psychotic illness.

Depression
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). Also, because of the increased risk for intentional overdose in patients with depression in general, the quantity of a medicinal product, including zaleplon, prescribed for such patients should be kept to the necessary minimum.

Zerene 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

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 (see section 4.7).

Combination with other CNS-acting compounds should be taken into account. Enhancement of the central sedation may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anti-epileptic medicinal products, anaesthetics, and sedative antihistamines.

Coadministration of a single zaleplon 10 mg dose and venlafaxine (extended release) 75 mg or 150 mg daily did not produce any interaction on memory (immediate and delayed word recall) or psychomotor performance (digit symbol substitution test). Additionally, there was no pharmacokinetic interaction between zaleplon and venlafaxine (extended release).

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

Cimetidine, a non-specific moderate inhibitor of several hepatic enzymes including both aldehyde oxidase and CYP3A4, produced an 85% increase in plasma concentrations of zaleplon because it inhibited both the primary (aldehyde oxidase) and secondary (CYP3A4) enzymes responsible for zaleplon's metabolism. Therefore, caution is advisable in co-administering cimetidine and Zerene.

Co-administration of Zerene with a single 800 mg dose of erythromycin, a strong, selective CYP3A4 inhibitor, produced a 34% increase in zaleplon's plasma concentrations. A routine dosage adjustment of Zerene is not considered necessary, but patients should be advised that the sedative effects might be enhanced.

In contrast, rifampicin, a strong inducer of several hepatic enzymes, including CYP3A4 resulted in a four-fold reduction in zaleplon plasma concentration. Co-administration of Zerene together with inducers of CYP3A4 such as rifampicin, carbamazepine and phenobarbitone, may result in a reduction of zaleplon's efficacy.

Zerene did not affect the pharmacokinetic and pharmacodynamic profiles of digoxin and warfarin, two compounds with a narrow therapeutic index. In addition, ibuprofen, as an example of compounds that alter renal excretion, showed no interaction with Zerene.

4.6 Pregnancy and lactation

Although animal studies have shown no teratogenic or embryotoxic effects, insufficient clinical data

are available on Zerene to assess its safety during pregnancy and breastfeeding. Use of Zerene is not recommended during pregnancy. If the medicinal product is prescribed to a woman of child-bearing potential, she should be warned to contact her physician regarding discontinuance of the medicinal product if she intends to become or suspects that she is pregnant.

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

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

Because zaleplon is excreted in the breast milk, Zerene should not be administered to breast-feeding mothers.

4.7 Effects on ability to drive and use machines

Zerene has major influence on the ability to drive and use machines.
Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive or to use machines. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased (see section 4.5). Caution is recommended for patients performing skilled tasks.

4.8 Undesirable effects

The most frequent reported adverse drug reactions are amnesia, paraesthesia, somnolence and dysmenorrhea.

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)
Very rare (<1/10,000)
not known (cannot be estimated from the available data)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Organ/System (Frequency)	**Adverse Reactions**
Nervous system disorders	
Common:	amnesia, paraesthesia, somnolence
Uncommon:	ataxia/coordination abnormal, dizziness, disturbance in attention, parosmia, speech disorder (dysarthria, slurred speech), hypoaesthesia
See also below under Amnesia	
Eye disorders	
Uncommon:	visual impairment, diplopia
Ear and labyrinth disorders	
Uncommon:	hyperacusis

Gastrointestinal disorders	
Uncommon:	nausea
Skin and subcutaneous tissue disorders	
Uncommon:	photosensitivity reaction
Frequency not known:	angioedema
Metabolism and nutrition disorders	
Uncommon:	anorexia
General disorders and administration site conditions	
Uncommon:	asthenia, malaise
Immune system disorders	
Very rare:	anaphylactic/anaphylactoid reactions
Hepatobiliary disorders	
Frequency not known:	hepatotoxicity (mostly described as transaminase increased)
Reproductive system and breast disorders	
Common:	dysmenorrhea
Psychiatric disorders	
Uncommon:	depersonalisation, hallucinations, depression, confusional state, apathy
Frequency not known:	somnambulism

See also below under Depression and Psychiatric and "paradoxical" reactions

Amnesia
Anterograde amnesia may occur using recommended therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour (see section 4.4).

Depression
Pre-existing depression may be unmasked during benzodiazepine or benzodiazepine-like agent use.

Psychiatric and "paradoxical" reactions
Reactions like restlessness, agitation, irritability, decreased inhibition, aggressiveness, abnormal thinking, delusions, rages, nightmares, depersonalisation, hallucinations, psychoses, inappropriate behaviour, extroversion that seems out of character, and other adverse behavioural reactions are known to occur when using benzodiazepines or benzodiazepine-like agents. Such reactions are more likely to occur in the elderly.

Dependence
Use (even at therapeutic doses) may lead to the development of physical dependence: discontinuation of therapy may result in withdrawal or rebound phenomena (see section 4.4). Psychic dependence may occur. Abuse of benzodiazepines and benzodiazepine-like active substances has been reported.

4.9 Overdose

There is limited clinical experience with the effects of an acute overdose of Zerene, and overdose levels in humans have not been determined.

As with other benzodiazepines or benzodiazepine-like agents, overdose should not present a threat to life unless combined with other CNS depressants (including alcohol).

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

Following overdose with oral benzodiazepine or benzodiazepine-like agents, vomiting should be induced (within one hour) if the patient is conscious or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce the absorption. Special attention should be paid to respiratory or cardiovascular functions in intensive care.

Overdose of benzodiazepine or benzodiazepine-like agents is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion, and lethargy, in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death.

Chromaturia (blue-green urine discolouration) has been reported with zaleplon overdose.

Flumazenil may be useful as an antidote. Animal studies suggest that flumazenil is an antagonist to zaleplon and should be considered in the management of Zerene overdose. However, there is no clinical experience with the use of flumazenil as an antidote to a Zerene overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Benzodiazepine related drugs, ATC Code N05CF03

Zaleplon is a pyrazolopyrimidine hypnotic that is structurally different from benzodiazepines and other hypnotics. Zaleplon binds selectively to the benzodiazepine type I receptor.

Zaleplon's pharmacokinetic profile shows rapid absorption and elimination (see section 5.2). In combination with its subtype selective receptor-binding characteristics, with high selectivity and low affinity for the benzodiazepine type I receptor, these properties are responsible for the overall characteristics of Zerene.

Zerene's efficacy has been demonstrated in both sleep laboratory studies using objective polysomnography (PSG) measures of sleep and in outpatient studies using patient questionnaires to assess sleep. In these studies, patients were diagnosed with primary (psychophysiological) insomnia.

Sleep latency in outpatient studies was decreased for up to 4 weeks in non-elderly patients with Zerene 10 mg. In elderly patients, sleep latency was often significantly decreased with Zerene 5 mg and was consistently decreased with Zerene 10 mg compared with placebo in 2-week studies. This decreased sleep latency was significantly different from that observed with placebo. Results from the 2- and 4-week studies showed that no pharmacological tolerance developed with any dose of Zerene.

In Zerene studies using objective PSG measures, Zerene 10 mg was superior to placebo in decreasing sleep latency and increasing sleep duration during the first half of the night. Zerene has been shown to preserve sleep stages in controlled studies that measured the percentage of sleep time spent in each sleep stage.

5.2 Pharmacokinetic properties

Absorption
Zaleplon is rapidly and almost completely absorbed after oral administration, and peak concentrations are reached in approximately 1 hour. At least 71% of the orally-administered dose is absorbed. Zaleplon undergoes presystemic metabolism, resulting in an absolute bioavailability of approximately 30%.

Distribution
Zaleplon is lipophilic with a volume of distribution of about 1.4±0.3 l/kg following intravenous administration. The *in vitro* plasma protein binding is approximately 60%, suggesting little risk of active substance interaction due to protein binding.

Metabolism
Zaleplon is primarily metabolised by aldehyde oxidase to form 5-oxo-zaleplon. Additionally, zaleplon is metabolised by CYP3A4 to form desethylzaleplon which is further metabolised by aldehyde oxidase to form 5-oxo-desethylzaleplon. The oxidative metabolites are further metabolised by conjugation via glucuronidation. All of zaleplon's metabolites are inactive in both animal behavioural models and *in vitro* activity assays.

Zaleplon plasma concentrations increased linearly with dose, and zaleplon showed no signs of accumulation following administration of up to 30 mg/day. The elimination half-life of zaleplon is approximately 1 hour.

Excretion
Zaleplon is excreted in the form of inactive metabolites, mainly in the urine (71%) and faeces (17%). Fifty-seven percent (57%) of the dose is recovered in urine in the form of 5-oxo-zaleplon and its glucuronide metabolite, an additional 9% is recovered as 5-oxo-desethylzaleplon and its glucuronide metabolite. The remainder of the urinary recovery consists of minor metabolites. The majority of the faecal recovery consists of 5-oxo-zaleplon.

Hepatic Impairment
Zaleplon is metabolised primarily by the liver and undergoes significant presystemic metabolism. Consequently, the oral clearance of zaleplon was reduced by 70% and 87% in compensated and decompensated cirrhotic patients, respectively, leading to marked increases in mean C_{max} and AUC (up to 4-fold and 7-fold in compensated and decompensated patients, respectively) relative to healthy subjects. The dose of zaleplon should be reduced in patients with mild to moderate hepatic impairment, and zaleplon is not recommended for use in patients with severe hepatic impairment.

Renal Impairment
The single dose pharmacokinetics of zaleplon were studied in patients with mild (creatinine clearance 40 to 89 ml/min) and moderate (20 to 39 ml/min) renal impairment, and in patients on dialysis. In patients with moderate impairment and those on dialysis there was a reduction of approximately 23% in peak plasma concentration compared to healthy volunteers. The extent of exposure to zaleplon was similar among all groups. Therefore, no dose adjustment is necessary in patients with mild to moderate renal impairment. Zaleplon has not been adequately studied in patients with severe renal impairment.

5.3 Preclinical safety data

Repeated oral administration of zaleplon to rats and dogs elicited increases in liver and adrenal weights; however, these increases occurred at high multiples of the maximum therapeutic dose, were reversible, were not associated with degenerative microscopic changes in liver or adrenal glands, and were consistent with effects in animals with other compounds that bind to benzodiazepine receptors. In a three month study in prepubescent dogs there was significant reduction in the weight of both prostate and testes at high multiples of the maximum therapeutic dose. Oral administration of zaleplon

to rats for 104 consecutive weeks at dosage levels up to 20 mg/kg/day did not result in compound-related tumorigenicity. Oral administration of zaleplon to mice for 65 or 104 consecutive weeks at high dosage levels (≥100 mg/kg/day) elicited a statistically significant increase in benign but not in malignant liver tumors. The increased incidence of benign liver tumors in mice was likely an adaptive event.

Overall, the results of the preclinical studies do not suggest any significant safety hazard for use of Zerene at recommended doses in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule core
Microcrystalline cellulose,
pregelatinised starch,
silicon dioxide,
sodium lauryl sulphate,
magnesium stearate,
lactose monohydrate,
indigo carmine (E132),
titanium dioxide (E171).

Capsule shell
gelatin,
titanium dioxide (E171),
red iron oxide (E172),
yellow iron oxide (E172),
black iron oxide (E172),
sodium lauryl sulphate,
silicon dioxide.

Printing inks on the shell contain the following (gold ink S-13050):
shellac,
lecithin,
simethicone,
yellow iron oxide (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

PVC / PVDC aluminium blister packages of 7, 10, 14 capsules in perforated unit-dose blisters**.** Not all pack sizes may be marketed.

6.6 Special precautions for disposal and handling

No special requirements.

Zerene has been designed so that if the contents of the capsule are dissolved in a liquid, the liquid will change colour and become cloudy.

7. MARKETING AUTHORISATION HOLDER

Meda AB
Pipers väg 2A
S-170 09 Solna
Sweden

8. MARKETING AUTHORISATION NUMBERS

EU/1/99/099/001-003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 12 March 1999
Date of latest renewal: 12 March 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

Zerene 10 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 10 mg of zaleplon.

Excipients: Lactose monohydrate 49 mg.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard.
Capsules have an opaque white hard shell with pink band, "W" and the strength "10 mg".

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4.1 Therapeutic indications

Zerene is indicated for the treatment of patients with insomnia who have difficulty falling asleep. It is indicated only when the disorder is severe, disabling or subjecting the individual to extreme distress.

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For adults, the recommended dose is 10 mg.

Treatment should be as short as possible with a maximum duration of two weeks**.**

Zerene can be taken immediately before going to bed or after the patient has gone to bed and is experiencing difficulty falling asleep. As administration after food delays the time to maximal plasma concentration by approximately 2 hours no food should be eaten with or shortly before intake of Zerene.

The total daily dose of Zerene should not exceed 10 mg in any patient. Patients should be advised not to take a second dose within a single night.

Elderly
Elderly patients may be sensitive to the effects of hypnotics; therefore, 5 mg is the recommended dose of Zerene.

Paediatric patients
Zerene is contraindicated in children (see section 4.3).

Hepatic impairment
As clearance is reduced, patients with mild to moderate hepatic impairment should be treated with Zerene 5 mg. For severe hepatic impairment see section 4.3.

Renal impairment
No dosage adjustment is required in patients with mild to moderate renal insufficiency, because Zerene pharmacokinetics is not altered in such patients. Severe renal impairment is contraindicated (see section 4.3.).

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Hypersensitivity to the active substance or to any of the excipients
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Renal impairment
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Caution should be observed when prescribing sedative medicinal products to patients with chronic respiratory insufficiency.

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Cimetidine, a non-specific moderate inhibitor of several hepatic enzymes including both aldehyde oxidase and CYP3A4, produced an 85% increase in plasma concentrations of zaleplon because it inhibited both the primary (aldehyde oxidase) and secondary (CYP3A4) enzymes responsible for zaleplon's metabolism. Therefore, caution is advisable in co-administering cimetidine and Zerene.

Co-administration of Zerene with a single 800 mg dose of erythromycin, a strong, selective CYP3A4 inhibitor, produced a 34% increase in zaleplon's plasma concentrations. A routine dosage adjustment of Zerene is not considered necessary, but patients should be advised that the sedative effects might be enhanced.

In contrast, rifampicin, a strong inducer of several hepatic enzymes, including CYP3A4 resulted in a four fold reduction in zaleplon plasma concentration. Co-administration of Zerene together with inducers of CYP3A4 such as rifampicin, carbamazepine and phenobarbitone, may result in a reduction of zaleplon's efficacy.

Zerene did not affect the pharmacokinetic and pharmacodynamic profiles of digoxin and warfarin, two compounds with a narrow therapeutic index. In addition, ibuprofen, as an example of compounds that alter renal excretion, showed no interaction with Zerene.

4.6 Pregnancy and lactation

Although animal studies have shown no teratogenic effects or embryotoxic effects, insufficient clinical data are available on Zerene to assess its safety during pregnancy and breastfeeding. Use of Zerene is not recommended during pregnancy. If the medicinal product is prescribed to a woman of child-bearing potential, she should be warned to contact her physician regarding discontinuance of the medicinal product if she intends to become or suspects that she is pregnant.

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

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

Because zaleplon is excreted in the breast milk, Zerene should not be administered to breast-feeding mothers.

4.7 Effects on ability to drive and use machines

Zerene has major influence on the ability to drive and use machines.
Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive or to use machines. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased (see section 4.5). Caution is recommended for patients performing skilled tasks.

4.8 Undesirable effects

The most frequent reported adverse drug reactions are amnesia, paraesthesia, somnolence and dysmenorrhea.

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)
Very rare (<1/10,000)
not known (cannot be estimated from the available data)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Organ/System (Frequency)	**Adverse Reactions**
Nervous system disorders	
Common:	amnesia, paraesthesia, somnolence
Uncommon:	ataxia/coordination abnormal, dizziness, disturbance in attention, parosmia, speech disorder (dysarthria, slurred speech), hypoaesthesia

See also below under Amnesia

Eye disorders	
Uncommon:	visual impairment, diplopia

Ear and labyrinth disorders	
Uncommon:	hyperacusis
Gastrointestinal disorders	
Uncommon:	nausea
Skin and subcutaneous tissue disorders	
Uncommon:	photosensitivity reaction
Frequency not known:	angioedema
Metabolism and nutrition disorders	
Uncommon:	anorexia
General disorders and administration site conditions	
Uncommon:	asthenia, malaise
Immune system disorders	
Very rare:	anaphylactic/anaphylactoid reactions
Hepatobiliary disorders	
Frequency not known:	hepatotoxicity (mostly described as transaminase increased)
Reproductive system and breast disorders	
Common:	dysmenorrhea
Psychiatric disorders	
Uncommon:	depersonalisation, hallucinations, depression, confusional state, apathy
Frequency not known:	somnambulism

See also below under Depression and Psychiatric and "paradoxical" reactions

Amnesia
Anterograde amnesia may occur using recommended therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour (see section 4.4).

Depression
Pre-existing depression may be unmasked during benzodiazepine or benzodiazepine-like agent use.

Psychiatric and "paradoxical" reactions
Reactions like restlessness, agitation, irritability, decreased inhibition, aggressiveness, abnormal thinking, delusions, rages, nightmares, depersonalisation, hallucinations, psychoses, inappropriate behaviour, extroversion that seems out of character and other adverse behavioural reactions are known to occur when using benzodiazepines or benzodiazepine-like agents. Such reactions are more likely to occur in the elderly.

Dependence
Use (even at therapeutic doses) may lead to the development of physical dependence: discontinuation of therapy may result in withdrawal or rebound phenomena (see section 4.4). Psychic dependence may occur. Abuse of benzodiazepines and benzodiazepine-like active substances has been reported.

4.9 Overdose

There is limited clinical experience with the effects of an acute overdose of Zerene, and overdose levels in humans have not been determined.

As with other benzodiazepines or benzodiazepine-like agents, overdose should not present a threat to life unless combined with other CNS depressants (including alcohol).

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

Following overdose with oral benzodiazepine or benzodiazepine-like agents, vomiting should be induced (within one hour) if the patient is conscious or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce the absorption. Special attention should be paid to respiratory or cardiovascular functions in intensive care.

Overdose of benzodiazepine or benzodiazepine-like agents is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion, and lethargy, in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death.

Chromaturia (blue-green urine discolouration) has been reported with zaleplon overdose.

Flumazenil may be useful as an antidote. Animal studies suggest that flumazenil is an antagonist to zaleplon and should be considered in the management of Zerene overdose. However, there is no clinical experience with the use of flumazenil as an antidote to a Zerene overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Benzodiazepine related drugs, ATC Code N05CF03

Zaleplon is a pyrazolopyrimidine hypnotic that is structurally different from benzodiazepines and other hypnotics. Zaleplon binds selectively to the benzodiazepine type I receptor.

Zaleplon's pharmacokinetic profile shows rapid absorption and elimination (see section 5.2). In combination with its subtype selective receptor-binding characteristics, with high selectivity and low affinity for the benzodiazepine type I receptor, these properties are responsible for the overall characteristics of Zerene.

Zerene's efficacy has been demonstrated in both sleep laboratory studies using objective polysomnography (PSG) measures of sleep and in outpatient studies using patient questionnaires to assess sleep. In these studies, patients were diagnosed with primary (psychophysiological) insomnia.

Sleep latency in outpatient studies was decreased for up to 4 weeks in non-elderly patients with Zerene 10 mg. In elderly patients, sleep latency was often significantly decreased with Zerene 5 mg and was consistently decreased with Zerene 10 mg compared with placebo in 2-week studies. This decreased sleep latency was significantly different from that observed with placebo. Results from the 2- and 4-week studies showed that no pharmacological tolerance developed with any dose of Zerene.

In Zerene studies using objective PSG measures, Zerene 10 mg was superior to placebo in decreasing sleep latency and increasing sleep duration during the first half of the night. Zerene has been shown to

preserve sleep stages in controlled studies that measured the percentage of sleep time spent in each sleep stage.

5.2 Pharmacokinetic properties

Absorption
Zaleplon is rapidly and almost completely absorbed after oral administration, and peak concentrations are reached in approximately 1 hour. At least 71% of the orally-administered dose is absorbed. Zaleplon undergoes presystemic metabolism, resulting in an absolute bioavailability of approximately 30%.

Distribution
Zaleplon is lipophilic with a volume of distribution of about 1.4 ± 0.3 l/kg following intravenous administration. The *in vitro* plasma protein binding is approximately 60%, suggesting little risk of active substance interaction due to protein binding.

Metabolism
Zaleplon is primarily metabolised by aldehyde oxidase to form 5-oxo-zaleplon. Additionally, zaleplon is metabolised by CYP3A4 to form desethylzaleplon which is further metabolised by aldehyde oxidase to form 5-oxo-desethylzaleplon. The oxidative metabolites are further metabolised by conjugation via glucuronidation. All of zaleplon's metabolites are inactive in both animal behavioural models and *in vitro* activity assays.

Zaleplon plasma concentrations increased linearly with dose, and zaleplon showed no signs of accumulation following administration of up to 30 mg/day. The elimination half-life of zaleplon is approximately 1 hour.

Excretion
Zaleplon is excreted in the form of inactive metabolites, mainly in the urine (71%) and faeces (17%). Fifty-seven percent (57%) of the dose is recovered in urine in the form of 5-oxo-zaleplon and its glucuronide metabolite, an additional 9% is recovered as 5-oxo-desethylzaleplon and its glucuronide metabolite. The remainder of the urinary recovery consists of minor metabolites. The majority of the faecal recovery consists of 5-oxo-zaleplon.

Hepatic Impairment
Zaleplon is metabolized primarily by the liver and undergoes significant presystemic metabolism. Consequently, the oral clearance of zaleplon was reduced by 70% and 87% in compensated and decompensated cirrhotic patients, respectively, leading to marked increases in mean C_{max} and AUC (up to 4-fold and 7-fold in compensated and decompensated patients, respectively) relative to healthy subjects. The dose of zaleplon should be reduced in patients with mild to moderate hepatic impairment, and zaleplon is not recommended for use in patients with severe hepatic impairment.

Renal Impairment
The single dose pharmacokinetics of zaleplon were studied in patients with mild (creatinine clearance 40 to 80 ml/min) and moderate (20 to 39 ml/min) renal impairment, and in patients on dialysis. In patients with moderate impairment and those on dialysis there was a reduction of approximately 23% in peak plasma concentration compared to healthy volunteers. The extent of exposure to zaleplon was similar among all groups. Therefore, no dose adjustment is necessary in patients with mild to moderate renal impairment. Zaleplon has not been adequately studied in patients with severe renal impairment.

5.3 Preclinical safety data

Repeated oral administration of zaleplon to rats and dogs elicited increases in liver and adrenal weights; however, these increases occurred at high multiples of the maximum therapeutic dose, were reversible, were not associated with degenerative microscopic changes in liver or adrenal glands, and were consistent with effects in animals with other compounds that bind to benzodiazepine receptors.

In a three month study in prepubescent dogs there was significant reduction in the weight of both prostate and testes at high multiples of the maximum therapeutic dose. Oral administration of zaleplon to rats for 104 consecutive weeks at dosage levels up to 20 mg/kg/day did not result in compound-related tumorigenicity. Oral administration of zaleplon to mice for 65 or 104 consecutive weeks at high dosage levels (≥100 mg/kg/day) elicited a statistically significant increase in benign but not in malignant liver tumors. The increased incidence of benign liver tumors in mice was likely an adaptive event.

Overall, the results of the preclinical studies do not suggest any significant safety hazard for use of Zerene at recommended doses in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule core
Microcrystalline cellulose,
pregelatinised starch,
silicon dioxide,
sodium lauryl sulphate,
magnesium stearate,
lactose monohydrate,
indigo carmine (E132),
titanium dioxide (E171).

Capsule shell
gelatin,
titanium dioxide (E171),
sodium lauryl sulphate,
silicon dioxide.

Printing inks on the shell contain the following (pink ink SW-1105):
shellac,
titanium dioxide (E171),
ammonium hydroxide,
red iron oxide (E172),
yellow iron oxide (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

PVC / PVDC aluminium blister packages of 7, 10, 14 capsules in perforated unit-dose blisters**.** Not all pack sizes may be marketed.

6.6 Special precautions for disposal and handling

No special requirements.

Zerene has been designed so that if the contents of the capsule are dissolved in a liquid, the liquid will change colour and become cloudy.

7. MARKETING AUTHORISATION HOLDER

Meda AB
Pipers väg 2A
S-170 09 Solna
Sweden

8. MARKETING AUTHORISATION NUMBERS

EU/1/99/099/004-006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 12 March 1999
Date of latest renewal: 12 March 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/.

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

MEDA Manufacturing GmbH
Neurather Ring 1
51063 Cologne
Germany

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON, TEXT FOR ZERENE 5 MG – PACK SIZES 7, 10 AND 14 CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Zerene 5 mg hard capsules
zaleplon

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 5 mg zaleplon

3. LIST OF EXCIPIENTS

Also contains: lactose monohydrate
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 hard capsules
10 hard capsules
14 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30ºC.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS

OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Meda AB
Pipers väg 2A
S-170 09 Solna
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/099/001 7 capsules
EU/1/99/099/002 10 capsules
EU/1/99/099/003 14 capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zerene 5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
5 MG CAPSULE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Zerene 5 mg hard capsules
zaleplon

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Meda AB

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON, TEXT FOR ZERENE 10 MG – PACK SIZES 7, 10 AND 14 CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Zerene 10 mg hard capsules
zaleplon

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 10 mg zaleplon

3. LIST OF EXCIPIENTS

Also contains: lactose monohydrate
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 hard capsules
10 hard capsules
14 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30ºC.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS

OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Meda AB
Pipers väg 2A
S-170 09 Solna
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/099/004 7 capsules
EU/1/99/099/005 10 capsules
EU/1/99/099/006 14 capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zerene 10 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
10 MG CAPSULE BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Zerene 10 mg hard capsules
zaleplon

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Meda AB

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Zerene 5 mg hard capsules
zaleplon

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT ZERENE IS AND WHAT IT IS USED FOR

Zerene belongs to a class of substances called benzodiazepine-related medicinal products, which consists of preparations with hypnotic actions.

Zerene will help you to sleep. Sleeping problems do not usually last long, and most people only need a short course of treatment. The duration of treatment should usually vary from a few days to two weeks. If you still have problems sleeping after you have finished your capsules, contact your doctor again.

2. BEFORE YOU TAKE ZERENE

Do not take Zerene if you have

- hypersensitivity (an allergy) to zaleplon or to any other ingredients of Zerene
- sleep apnoea syndrome (stopping breathing for short periods while asleep)
- severe kidney or liver problems
- myasthenia gravis (very weak or tired muscles)
- severe breathing or chest problems

If you are in any doubt about whether you have any of these conditions, do ask your doctor.
Children under 18 years of age must not take Zerene.

Take special care with Zerene

- Never drink alcohol while you are being treated with Zerene. Alcohol can increase the undesirable effects of any medicine taken to help you sleep.
- Use with extreme caution if you have ever been addicted to medicines or alcohol.
- If you are taking any medicines belonging to the sleep inducing group, including Zerene, there is a possibility that you may become dependent on them. Once physical dependence has developed, abrupt termination of treatment may be accompanied by withdrawal symptoms. These may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability.

- Do not use Zerene or any other sleeping medicine for longer than your doctor tells you to.
- Do not use a second dose of Zerene within a single night.
- If your sleeplessness persists or worsens after a short course of Zerene treatment contact your doctor.
- There is a chance that you may experience a certain type of temporary memory loss (amnesia) and lack of coordination when taking sleep medicines. This can usually be avoided if you remain inactive for at least 4 hours after taking Zerene.
- There is a chance that you may experience somnambulism (sleepwalking), including eating or driving while not fully awake with no memory of the event. If you experience these events, contact your doctor immediately.
- Reactions like restlessness, agitation, irritability, aggressiveness, abnormal thinking, delusion, rages, nightmares, depersonalisation, hallucinations, psychoses, inappropriate behaviour, extroversion that seems out of character and other behavioural effects have been reported following use of any medicines belonging to the sleep inducing group, including Zerene. These reactions may be active substance-induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. They are more likely to occur in the elderly. If you experience these events, contact your doctor immediately.
- Rare cases of severe allergic reactions have been reported. An allergic reaction may include a rash, itching, difficulty breathing or swelling of the face, lips, throat or tongue, or nausea and vomiting. If you experience any of these events, contact your doctor immediately.

Taking other medicines

Do not take any other medicines without asking your doctor or pharmacist first. This includes medicines that can be bought without a prescription. Some can cause drowsiness and should not be taken while taking Zerene.

When Zerene is taken with other medicines that act on the brain, the combination may make you more drowsy than it should. Be aware that such combinations may cause you to feel drowsy the next day. These medicines include: substances used in the treatment of mental conditions (antipsychotics, hypnotics, anxiolytics/sedatives, antidepressants), medicines used for strong pain relief (narcotic analgesics), medicines used for the treatment of seizures/convulsions (antiepileptic medicines), medicines used for loss of feeling/ insensibility (anaesthetics), and medicines used in the treatment of allergies (sedative antihistamines).

You should tell your doctor or pharmacist if you are taking cimetidine (a stomach medicine) or erythromycin (an antibiotic).

Taking Zerene with food and drink

It is not recommended that you take Zerene with or immediately after eating a large meal as it may work more slowly. Swallow the capsule(s) with a small glass of water. Never drink alcohol while you are being treated with Zerene (see "Take Special care with Zerene").

Pregnancy and breast-feeding

Tell your doctor if you are or intend to become pregnant. Zerene should not be taken at these times because there are not enough clinical data available to assess its safety during pregnancy.

Tell your doctor if you are breast-feeding. Zerene should not be taken at this time because there is not enough clinical data available to assess its safety during breast-feeding.

Driving and using machines

Zerene may make you feel drowsy, cause loss of concentration or memory or muscle weakness. This feeling may be even worse when you sleep for less than 7 to 8 hours after taking your medication. If affected do not drive or operate machinery.

Important information about some of the ingredients of Zerene

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE ZERENE

Always take Zerene exactly as your doctor has told you. You should check with your doctor if you are not sure.

The usual dose for adults is 10 mg just before going to bed, or after you have gone to bed and you are having difficulty falling asleep. You should not take a second dose within a single night.

There are different doses for people who are 65 or older, and those who have mild to moderate liver problems:

65 or older: Take one 5 mg capsule
Mild to moderate liver problems: Take one 5 mg capsule

Zerene has been designed, so that if the contents of the capsule are dissolved in liquid, the liquid will change colour and become cloudy.

If you take more Zerene than you should

Contact a doctor immediately and say how many capsules you have taken. Do not go unaccompanied to seek medical help.

If an overdose has been taken you may become increasingly drowsy very quickly, with high doses probably leading to a coma.

If you forget to take Zerene

Just take your next capsule at the usual time, then go on as before. Do not try and catch up on the doses you have missed.

If you stop taking Zerene

On stopping treatment, your original sleeplessness may return and you may experience symptoms such as mood changes, anxiety, and restlessness. If you suffer from these symptoms, ask your doctor for advice.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Zerene can cause side effects, although not everybody gets them. If you notice any of the following, or any other changes in your health, do tell your doctor as soon as possible.

The frequency of possible side effects listed below is defined using the following convertion:

very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)
not known (frequency cannot be estimated from the available data)

Like all medicines, Zerene can cause side effects, although not everybody gets them. If you notice any of the following, or any other changes in your health, do tell your doctor as soon as possible.

Side effects that may occur commonly: drowsiness; memory difficulties; sensations like tingling, e.g. in the extremities (paraesthesia); painful menstruation.

Uncommon side effects include: dizziness; weakness; reduced coordination of movements; unsteadiness and/or falls (ataxia); decreased concentration; apathy; restlessness; depression; agitation; irritability; confusion, abnormal thinking and behaviour (extroversion that seems out of character, decreased inhibition, aggressiveness, rages, delusion, depersonalisation, psychosis); nightmares; hallucinations; double vision or other sight problems; increased sensitivity to noise (hyperacusis); smell disorder (parosmia); speech disorders, including slurred speech; numbness, e.g. in the extremities (hypoaesthesia); nausea; decreased appetite; increased sensitivity to light (sunlight, UV light); feeling vaguely ill (malaise).

In very rare cases, allergic reactions, some severe, sometimes with difficulty in breathing, have been reported and may require immediate medical care. An allergic reaction may also include a rash, itching, or swelling of the face, lips, throat or tongue.

Increases in transaminases (a group of liver enzymes occurring naturally in the blood) have been reported, which may be a sign of liver problems.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ZERENE

Keep out of the reach and sight of children.

Do not use Zerene after the expiry date, which is stated on the carton after EXP. The expiry date refers to the last day of that month.

Do not store above 30ºC.

If you have any further questions, please consult your doctor or pharmacist.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Zerene contains

The active substance in each Zerene hard capsule is zaleplon 5 mg.

The other ingredients are microcrystalline cellulose, pregelatinised starch, silicon dioxide, sodium lauryl sulphate, magnesium stearate, lactose monohydrate, indigo carmine (E132), titanium dioxide (E171).

Ingredients of the capsule shell: gelatin, titanium dioxide (E171), red iron oxide (E172), yellow iron oxide (E172), black iron oxide (E172), sodium lauryl sulphate and silicon dioxide. Printing inks on the shell contain the following (gold ink S-13050): shellac, lecithin, simethicone, yellow iron oxide (E172).

What Zerene looks like and contents of the pack

Zerene 5 mg hard capsules, which contain an intensely dark blue powder, have a light brown cap, with gold imprint "W", and white body, with gold imprint "5 mg". They are packed in blisters. Each pack contains 7, 10 or 14 hard capsules.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation holder:
Meda AB
Pipers väg 2A
S-170 09 Solna
Sweden

Manufacturer:
MEDA Manufacturing GmbH
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51063 Cologne
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Zerene 10 mg hard capsules
zaleplon

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT ZERENE IS AND WHAT IT IS USED FOR

Zerene belongs to a class of substances called benzodiazepine-related medicinal products, which consists of preparations with hypnotic actions.

Zerene will help you to sleep. Sleeping problems do not usually last long, and most people only need a short course of treatment. The duration of treatment should usually vary from a few days to two weeks. If you still have problems sleeping after you have finished your capsules, contact your doctor again.

2. BEFORE YOU TAKE ZERENE

Do not take Zerene if you have

- hypersensitivity (an allergy) to zaleplon or to any other ingredients of Zerene
- sleep apnoea syndrome (stopping breathing for short periods while asleep)
- severe kidney or liver problems
- myasthenia gravis (very weak or tired muscles)
- severe breathing or chest problems

If you are in any doubt about whether you have any of these conditions, do ask your doctor.
Children under 18 years of age must not take Zerene.

Take special care with Zerene

- Never drink alcohol while you are being treated with Zerene. Alcohol can increase the undesirable effects of any medicine taken to help you sleep.
- Use with extreme caution if you have ever been addicted to medicines or alcohol.
- If you are taking any medicines belonging to the sleep inducing group, including Zerene, there is a possibility that you may become dependent on them. Once physical dependence has developed, abrupt termination of treatment may be accompanied by withdrawal symptoms. These may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability.

- Do not use Zerene or any other sleeping medicine for longer than your doctor tells you to.
- Do not use a second dose of Zerene within a single night.
- If your sleeplessness persists or worsens after a short course of Zerene treatment contact your doctor.
- There is a chance that you may experience a certain type of temporary memory loss (amnesia) and lack of coordination when taking sleep medicines. This can usually be avoided if you remain inactive for at least 4 hours after taking Zerene.
- There is a chance that you may experience somnambulism (sleepwalking), including eating or driving while not fully awake with no memory of the event. If you experience these events, contact your doctor immediately.
- Reactions like restlessness, agitation, irritability, aggressiveness, abnormal thinking, delusion, rages, nightmares, depersonalisation, hallucinations, psychoses, inappropriate behaviour, extroversion that seems out of character and other behavioural effects have been reported following use of any medicines belonging to the sleep inducing group, including Zerene. These reactions may be active substance-induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. They are more likely to occur in the elderly. If you experience these events, contact your doctor immediately.
- Rare cases of severe allergic reactions have been reported. An allergic reaction may include a rash, itching, difficulty breathing or swelling of the face, lips, throat or tongue, or nausea and vomiting. If you experience any of these events, contact your doctor immediately.

Taking other medicines

Do not take any other medicines without asking your doctor or pharmacist first. This includes medicines that can be bought without a prescription. Some can cause drowsiness and should not be taken while taking Zerene.

When Zerene is taken with other medicines that act on the brain, the combination may make you more drowsy than it should. Be aware that such combinations may cause you to feel drowsy the next day. These medicines include: substances used in the treatment of mental conditions (antipsychotics, hypnotics, anxiolytics/sedatives, antidepressants), medicines used for strong pain relief (narcotic analgesics), medicines used for the treatment of seizures/convulsions (antiepileptic medicines), medicines used for loss of feeling/insensibility (anaesthetics), and medicines used in the treatment of allergies (sedative antihistamines).

You should tell your doctor or pharmacist if you are taking cimetidine (a stomach medicines) or erythromycin (an antibiotic).

Taking Zerene with food and drink

It is not recommended that you take Zerene with or immediately after eating a large meal as it may work more slowly. Swallow the capsule(s) with a small glass of water. Never drink alcohol while you are being treated with Zerene (see "Take Special care with Zerene").

Pregnancy and breast-feeding

Tell your doctor if you are or intend to become pregnant. Zerene should not be taken at these times because there are not enough clinical data available to assess its safety during pregnancy.

Tell your doctor if you are breast-feeding. Zerene should not be taken at this time because there are not enough clinical data available to assess its safety during breast-feeding.

Driving and using machines

Zerene may make you feel drowsy, cause loss of concentration or memory or muscle weakness. This feeling may be even worse when you sleep for less than 7 to 8 hours after taking your medication. If affected do not drive or operate machinery

Important information about some of the ingredients of Zerene

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE ZERENE

Always take Zerene exactly as your doctor has told you. You should check with your doctor if you are not sure.

The usual dose for adults is 10 mg just before going to bed, or after you have gone to bed and you are having difficulty falling asleep. You should not take a second dose within a single night.

There are different doses for people who are 65 or older, and those who have mild to moderate liver problems:

65 or older: Take one 5 mg capsule
Mild to moderate liver problems: Take one 5 mg capsule

Zerene has been designed, so that if the contents of the capsule are dissolved in liquid, the liquid will change colour and become cloudy.

If you take more Zerene than you should

Contact a doctor immediately and say how many capsules you have taken. Do not go unaccompanied to seek medical help.

If an overdose has been taken you may become increasingly drowsy very quickly, with high doses probably leading to a coma.

If you forget to take Zerene

Just take your next capsule at the usual time, then go on as before. Do not try and catch up on the doses you have missed.

If you stop taking Zerene

On stopping treatment, your original sleeplessness may return and you may experience symptoms such as mood changes, anxiety, and restlessness. If you suffer from these symptoms, ask your doctor for advice.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Zerene can cause side effects, although not everybody gets them. If you notice any of the following, or any other changes in your health, do tell your doctor as soon as possible.

The frequency of possible side effects listed below is defined using the following convertion:

very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)
not known (frequency cannot be estimated from the available data)

Like all medicines, Zerene can cause side effects, although not everybody gets them. If you notice any of the following, or any other changes in your health, do tell your doctor as soon as possible.

Side effects that may occur commonly: drowsiness; memory difficulties; sensations like tingling, e.g. in the extremities (paraesthesia); painful menstruation

Uncommon side effects include: dizziness; weakness; reduced coordination of movements; unsteadiness and/or falls (ataxia); decreased concentration; apathy; restlessness; depression; agitation; irritability; confusion; abnormal thinking and behaviour (extroversion that seems out of character, decreased inhibition, aggressiveness, rages, delusion, depersonalisation, psychosis); nightmares; hallucinations; double vision or other sight problems; increased sensitivity to noise (hyperacusis); smell disorder (parosmia); speech disorders, including slurred speech; numbness, e.g. in the extremities (hypoaesthesia); nausea; decreased appetite; increased sensitivity to light (sunlight, UV light); feeling vaguely ill (malaise).

In very rare cases, allergic reactions, some severe, sometimes with difficulty in breathing, have been reported and may require immediate medical care. An allergic reaction may also include a rash, itching, or swelling of the face, lips, throat or tongue.

Increases in transaminases (a group of liver enzymes occurring naturally in the blood) have been reported, which may be a sign of liver problems.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ZERENE

Keep out of the reach and sight of children.

Do not use Zerene after the expiry date which is stated on the carton after EXP. The expiry date refers to the last date of that month.

Do not store above 30ºC.

If you have any further questions, please consult your doctor or pharmacist.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Zerene contains

The active substance in each Zerene hard capsule is zaleplon 10 mg.

The other ingredients are microcrystalline cellulose, pregelatinised starch, silicon dioxide, sodium lauryl sulphate, magnesium stearate, lactose monohydrate, indigo carmine (E132), titanium dioxide (E171).

Ingredients of the capsule shell: gelatin, titanium dioxide (E171), sodium lauryl sulphate and silicon dioxide. Printing inks on the shell contain the following (pink ink SW-1105): shellac, titanium dioxide (E171), ammonium hydroxide, red iron oxide (E172), yellow iron oxide (E172).

What Zerene looks like and contents of the pack

Zerene 10 mg hard capsules, which contain an intensely dark blue powder, have a white cap, with pink imprint "W", and white body, with pink imprint "10 mg". They are packed in blisters. Each pack contains 7, 10 or 14 hard capsules.
Not all pack sizes may be marketed.

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