ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Sonata 5 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 5 mg of zaleplon.

Excipient with known effect: Lactose monohydrate 54 mg.

For the 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 the strength "5 mg".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sonata 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**.**

Sonata 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 Sonata.

The total daily dose of Sonata 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 Sonata.

Paediatric patients
Sonata is contraindicated in children and adolescents under 18 years of age (see section 4.3).

Hepatic impairment
As clearance is reduced, patients with mild to moderate hepatic impairment should be treated with Sonata 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 Sonata 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 listed in section 6.1.
Severe hepatic impairment
Severe renal impairment
Sleep apnoea syndrome
Myasthenia gravis
Severe respiratory insufficiency
Children and adolescents (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 sedativehypnotics. 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 Sonata with medicinal products known to influence CYP3A4 is expected to result in changes in zaleplon's plasma concentrations. (See section 4.5).

Concomitant intake with alcohol is not recommended. The sedative effect may be enhanced when the product is used in combination with alcohol which may affect the ability to drive or use machines the next day (see section 4.7).

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 Sonata (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
Sonata 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.

Sonata 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 which may affect the ability to drive or use machines the next day (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. Concomitant use of zaleplon with these drugs may increase the risk of next day drowsiness, including impaired driving ability (see section 4.7).

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.

Diphenhydramine is reported to be a weak inhibitor of aldehyde oxidase in rat liver, but its inhibitory effects in human liver are not known. There is no pharmacokinetic interaction between zaleplon and diphenhydramine following the administration of a single dose (10 mg and 50 mg, respectively) of each drug. However, because both of these compounds have CNS effects, an additive pharmacodynamic effect is possible.

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 Sonata.

Co-administration of Sonata 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 Sonata 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 Sonata together with inducers of CYP3A4 such as rifampicin, carbamazepine and phenobarbitone, may result in a reduction of zaleplon's efficacy.

Sonata 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 Sonata.

4.6 Fertility, pregnancy and lactation

Although animal studies have shown no teratogenic or embryotoxic effects, insufficient clinical data are available on Sonata to assess its safety during pregnancy and breastfeeding. Use of Sonata 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, Sonata should not be administered to breast-feeding mothers.

4.7 Effects on ability to drive and use machines

Sonata 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 the next day. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased. Furthermore, the co-administration of zaleplon with alcohol and other CNS depressants increases this risk (see section 4.5). Caution is recommended for patients performing skilled tasks. Patients should be advised not to drive or operate machinery until it is established that their performance is not impaired.

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.

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 national reporting system listed in Appendix V.

4.9 Overdose

There is limited clinical experience with the effects of an acute overdose of Sonata, 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).

Symptoms of overdose
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.

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

Treatment of Sonata overdose is largely supportive. Attention to airway patency and supportive management of ventilation and haemodynamics are usually sufficient. In mild cases patients should sleep under control of respiratory and circulatory function. Induced vomiting is not recommended. In severe cases, use of activated charcoal or gastric lavage may be useful when performed soon after ingestion. Further, stabilization of circulatory function and intensive monitoring may be required. The value of forced dialysis or haemodialysis in the treatment of over dosage has not been determined.

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

Sonata'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 Sonata 10 mg. In elderly patients, sleep latency was often significantly decreased with Sonata 5 mg and was consistently decreased with Sonata 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 Sonata.

In Sonata studies using objective PSG measures, Sonata 10 mg was superior to placebo in decreasing sleep latency and increasing sleep duration during the first half of the night. Sonata 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 dose toxicity
In line with effects observed with other compounds binding to benzodiazepine receptors, reversible increases in liver and adrenal weights in rats and dogs were only noted upon repeated oral administration of high multiples of the maximum human therapeutic dose. At these doses, a significant reduction in the weight of both prostate and testes was apparent in a three month study in prepubescent dogs.

Reproduction toxicity
In a fertility and reproductive performance study in rats, mortality and decreased fertility were observed in males and females at an oral zaleplon dose of 100 mg/kg/day (equivalent to 49-times the maximum recommended human dose (MRHD) of 20 mg on a mg/m^2 basis). Follow-up studies indicated that impaired fertility was due to an effect on the female.

In embryofetal development studies, oral administration of zaleplon up to 100 mg/kg/day and 50 mg/kg/day to pregnant rats and rabbits, respectively, produced no evidence of teratogenicity (equivalent to 49- (rat) and 48-(rabbit) times the MRHD on a mg/m^2 basis). Pre-and postnatal growth of rats was reduced at the maternally toxic dose of 100 mg/kg/day. The no-effect dose for growth of rat offspring was 10 mg/kg (equivalent to 5-times the MRHD on a mg/m^2 basis). No adverse effects on embryofetal development were observed in rabbits.

In a pre- and postnatal development study in rats, increased stillbirth and postnatal mortality, and decreased growth and physical development, were observed in the offspring of females treated with doses of ≥7 mg/kg/day that did not elicit maternal toxicity. The no-effect dose for postnatal development was 1 mg/kg/day (equivalent to 0.5-times the MRHD on a mg/m^2 basis). In a subsequent cross-fostering study, adverse effects on offspring viability and growth appeared to result from both in utero and lactational exposure to zaleplon.

Carcinogenicity
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 Sonata 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,

Printing inks on the shell contain the following (gold ink SB-3002):
shellac,
ammonium hydroxide,
yellow iron oxide (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

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 other handling

No special requirements.

Sonata 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/1/99/102/001-003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE 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 http://www.ema.europa.eu/.

1. NAME OF THE MEDICINAL PRODUCT

Sonata 10 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 10 mg of zaleplon.

Excipient with known effect: Lactose monohydrate 49 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard.
Capsules have an opaque white hard shell with the strength “10 mg”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sonata 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**.**

Sonata 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 Sonata.

The total daily dose of Sonata 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 Sonata.

Paediatric patients
Sonata is contraindicated in children and adolescents under 18 years of age (see section 4.3).

Hepatic impairment
As clearance is reduced, patients with mild to moderate hepatic impairment should be treated with Sonata 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 Sonata 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 listed in section 6.1.
Severe hepatic impairment
Severe renal impairment
Sleep apnoea syndrome
Myasthenia gravis
Severe respiratory insufficiency
Children and adolescents (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 sedativehypnotics. 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 Sonata with medicinal products known to influence CYP3A4 is expected to result in changes in zaleplon's plasma concentrations. (See section 4.5).

Concomitant intake with alcohol is not recommended. The sedative effect may be enhanced when the product is used in combination with alcohol which may affect the ability to drive or use machines the next day (see section 4.7).

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 Sonata (see section 4.7).

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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
Sonata 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.

Sonata 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 which may affect the ability to drive or use machines the next day (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. Concomitant use of zaleplon with these drugs may increase the risk of next day drowsiness, including impaired driving ability (see section 4.7).

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.

Diphenhydramine is reported to be a weak inhibitor of aldehyde oxidase in rat liver, but its inhibitory effects in human liver are not known. There is no pharmacokinetic interaction between zaleplon and diphenhydramine following the administration of a single dose (10 mg and 50 mg, respectively) of each drug. However, because both of these compounds have CNS effects, an additive pharmacodynamic effect is possible.

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 Sonata.

Co-administration of Sonata 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 Sonata 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 Sonata together with inducers of CYP3A4 such as rifampicin, carbamazepine and phenobarbitone, may result in a reduction of zaleplon's efficacy.

Sonata 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 Sonata.

4.6 Fertility, pregnancy and lactation

Although animal studies have shown no teratogenic or embryotoxic effects, insufficient clinical data are available on Sonata to assess its safety during pregnancy and breastfeeding. Use of Sonata 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, Sonata should not be administered to breast-feeding mothers.

4.7 Effects on ability to drive and use machines

Sonata 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 the next day. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased. Furthermore, the co-administration of zaleplon with alcohol and other CNS depressants increases this risk (see section 4.5). Caution is recommended for patients performing skilled tasks. Patients should be advised not to drive or operate machinery until it is established that their performance is not impaired.

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.

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 national reporting system listed in Appendix V.

4.9 Overdose

There is limited clinical experience with the effects of an acute overdose of Sonata, 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).

Symptoms of overdose
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.

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

Treatment of Sonata overdose is largely supportive. Attention to airway patency and supportive management of ventilation and haemodynamics are usually sufficient. In mild cases patients should sleep under control of respiratory and circulatory function. Induced vomiting is not recommended. In severe cases, use of activated charcoal or gastric lavage may be useful when performed soon after ingestion. Further, stabilization of circulatory function and intensive monitoring may be required. The value of forced dialysis or haemodialysis in the treatment of over dosage has not been determined.

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

Sonata'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 Sonata 10 mg. In elderly patients, sleep latency was often significantly decreased with Sonata 5 mg and was consistently decreased with Sonata 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 Sonata.

In Sonata studies using objective PSG measures, Sonata 10 mg was superior to placebo in decreasing sleep latency and increasing sleep duration during the first half of the night. Sonata 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 dose toxicity
In line with effects observed with other compounds binding to benzodiazepine receptors, reversible increases in liver and adrenal weights in rats and dogs were only noted upon repeated oral administration of high multiples of the maximum human therapeutic dose. At these doses, a significant reduction in the weight of both prostate and testes was apparent in a three month study in prepubescent dogs.

Reproduction toxicity
In a fertility and reproductive performance study in rats, mortality and decreased fertility were observed in males and females at an oral zaleplon dose of 100 mg/kg/day (equivalent to 49-times the maximum recommended human dose (MRHD) of 20 mg on a mg/m^2 basis). Follow-up studies indicated that impaired fertility was due to an effect on the female.

In embryofetal development studies, oral administration of zaleplon up to 100 mg/kg/day and 50 mg/kg/day to pregnant rats and rabbits, respectively, produced no evidence of teratogenicity (equivalent to 49- (rat) and 48-(rabbit) times the MRHD on a mg/m^2 basis). Pre-and postnatal growth of rats was reduced at the maternally toxic dose of 100 mg/kg/day. The no-effect dose for growth of rat offspring was 10 mg/kg (equivalent to 5-times the MRHD on a mg/m^2 basis). No adverse effects on embryofetal development were observed in rabbits.

In a pre- and postnatal development study in rats, increased stillbirth and postnatal mortality, and decreased growth and physical development, were observed in the offspring of females treated with doses of ≥7 mg/kg/day that did not elicit maternal toxicity. The no-effect dose for postnatal development was 1 mg/kg/day (equivalent to 0.5-times the MRHD on a mg/m^2 basis). In a subsequent cross-fostering study, adverse effects on offspring viability and growth appeared to result from both in utero and lactational exposure to zaleplon.

Carcinogenicity
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 Sonata 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,

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

This medicinal product does not require any special temperature storage conditions.

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 other handling

No special requirements.

Sonata 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/1/99/102/004-006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE 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 http://www.ema.europa.eu/.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE
B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE
C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION
D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) 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 OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Periodic Safety Update Reports
The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. 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 SONATA 5 MG – PACK SIZES 7, 10 AND 14 CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Sonata 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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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/1/99/102/001 7 capsules
EU/1/99/102/002 10 capsules
EU/1/99/102/003 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

Sonata 5 mg

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

1. NAME OF THE MEDICINAL PRODUCT

Sonata 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 SONATA 10 MG – PACK SIZES 7, 10 AND 14 CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Sonata 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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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/1/99/102/004 7 capsules
EU/1/99/102/005 10 capsules
EU/1/99/102/006 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

Sonata 10 mg

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

1. NAME OF THE MEDICINAL PRODUCT

Sonata 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

Sonata 5 mg hard capsules
zaleplon

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- 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 signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Sonata is and what it is used for

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

Sonata 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. What you need to know before you take Sonata

Do not take Sonata

- if you are allergic to zaleplon or any of the other ingredients of this medicine (listed in section 6).
- if you have sleep apnoea syndrome (stopping breathing for short periods while asleep).
- if you have severe kidney or liver problems.
- if you have myasthenia gravis (very weak or tired muscles).
- if you have severe breathing or chest problems.

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

Warnings and precautions
Talk to your doctor or pharmacist before taking Sonata.
- Never drink alcohol while you are being treated with Sonata. 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 Sonata, 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 Sonata or any other sleeping medicine for longer than your doctor tells you to.
- Do not use a second dose of Sonata within a single night.
- If your sleeplessness persists or worsens after a short course of Sonata 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 Sonata.
- 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 Sonata. 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.

Children and adolescents
Do not give this medicine to children and adolescents under 18 years of age.

Other medicines and Sonata

Tell your doctor or pharmacist if you are taking, have recently taken or might take any 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 Sonata.

When Sonata 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). Drinking alcohol while being treated with Sonata may also cause you to feel drowsy the next day. Never drink alcohol while you are being treated with Sonata (see "Warnings and precautions").

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

Sonata with food, drink and alcohol

It is not recommended that you take Sonata 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 Sonata (see "Warnings and precautions").

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Sonata should not be taken at these times because there are not enough clinical data available to assess its safety during pregnancy and breast-feeding.

Driving and using machines

Sonata 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 or if you are already taking another central nervous system depressant or if you are drinking alcohol (see 'other medicines and Sonata'). If affected do not drive or operate machinery.

Sonata contains lactose.
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 Sonata

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist 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

Sonata 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 Sonata 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 Sonata

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 Sonata

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 medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine 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 convention:
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)

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.

Reporting of side effects
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5. How to store Sonata

Keep this medicine out of the sight and reach of children.

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

This medicinal product does not require any special temperature storage conditions.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Sonata contains

The active substance in each Sonata 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) and sodium lauryl sulphate. Printing inks on the shell contain the following (gold ink SB-3002): shellac, ammonium hydroxide, yellow iron oxide (E172).

What Sonata looks like and contents of the pack

Sonata 5 mg hard capsules, which contain a light blue powder, have a light brown cap 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.

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PACKAGE LEAFLET: INFORMATION FOR THE USER

Sonata 10 mg hard capsules
zaleplon

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- 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 signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Sonata is and what it is used for

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

Sonata 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. What you need to know before you take Sonata

Do not take Sonata

- if you are allergic to zaleplon or any of the other ingredients of this medicine (listed in section 6).
- if you have sleep apnoea syndrome (stopping breathing for short periods while asleep).
- if you have severe kidney or liver problems.
- if you have myasthenia gravis (very weak or tired muscles).
- if you have severe breathing or chest problems.

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

Warnings and precautions
Talk to your doctor or pharmacist before taking Sonata.
- Never drink alcohol while you are being treated with Sonata. 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 Sonata, 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 Sonata or any other sleeping medicine for longer than your doctor tells you to.
- Do not use a second dose of Sonata within a single night.
- If your sleeplessness persists or worsens after a short course of Sonata 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 Sonata.
- 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 Sonata. 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.

Children and adolescents
Do not give this medicine to children and adolescents under 18 years of age.

Other medicines and Sonata

Tell your doctor or pharmacist if you are taking, have recently taken or might take any 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 Sonata.

When Sonata 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). Drinking alcohol while being treated with Sonata may also cause you to feel drowsy the next day. Never drink alcohol while you are being treated with Sonata (see "Warnings and precautions").

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

Sonata with food, drink and alcohol

It is not recommended that you take Sonata 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 Sonata (see "Warnings and precautions").

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Sonata should not be taken at these times because there are not enough clinical data available to assess its safety during pregnancy and breast-feeding.

Driving and using machines

Sonata 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 or if you are already taking another central nervous system depressant or if you are drinking alcohol (see 'other medicines and Sonata'). If affected do not drive or operate machinery.

Sonata contains lactose.
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 Sonata

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist 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

Sonata 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 Sonata 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 Sonata

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 Sonata

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 medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine 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 convention:
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)

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).

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This medicinal product does not require any special temperature storage conditions.

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Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Sonata contains

The active substance in each Sonata 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) and sodium lauryl sulphate. 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 Sonata looks like and contents of the pack

Sonata 10 mg hard capsules, which contain a light blue powder, have a white cap 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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Annex IV

Scientific conclusions and grounds recommending the variation to the terms of the Marketing Authorisation

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for zaleplon, the scientific conclusions of CHMP are as follows:

Literature articles regarding next day effects on driving and mental alertness were published during the reporting period which examined these effects with zaleplon and other agents of the class. While there were no significant findings in relation to zaleplon, a small number of cases have been reported in the post-marketing setting, although mostly in combination with other CNS depressant agents and at doses greater than 10mg.

Warnings already exist in the zaleplon product information however based on the available information the PRAC considered it prudent within this procedure to strengthen the wording in SmPC and PL to ensure clear information is available for patients and healthcare professionals given the potentially serious consequences of next day psychomotor impairment.

Therefore, in view of available data regarding next day effects on driving and mental alertness, the PRAC considered that changes to the product information were warranted.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds recommending the variation to the terms of the Marketing Authorisation

On the basis of the scientific conclusions for zaleplon the CHMP is of the opinion that the benefit-risk balance of the medicinal product containing zaleplon is favourable subject to the proposed changes to the product information

The CHMP recommends that the terms of the Marketing Authorisation should be varied.