SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT AND INTERNATIONAL NONPROPRIETARY NAME (INN)

▲ ZASAN film tablets 5 mg
▲ ZASAN film tablets 10 mg
Zolpidem

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZASAN 5 mg
Each tablet contains 5 mg of zolpidem as active substance.

ZASAN 10 mg
Each tablet contains 10 mg of zolpidem as active substance.

3. PHARMACEUTICAL FORM

Film-coated tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Tablets ZASAN are intended for short-term treatment of insomnia.
Benzodiazepines and related drugs are for the treatment of clinically significant insomnia.

4.2. Posology and method of administration

ZASAN tablets should be taken with liquid, just before sleeping or rest time.
Treatment should be as short as possible. The duration of treatment should be no more than a few days to two weeks, maximum four weeks, including the time of gradual dose reduction, if it is clinically appropriate.
Dose reduction should be adapted to each patient.
In exceptional circumstances, treatment may be longer than the maximum recommended duration of treatment, but only with a careful re-assessment of patient.

Adults
The drug should be taken at once and should not be taken again during the same night.
The recommended daily dose for adults is 10 mg, and should be taken just before going to bed.
The lowest effective daily dose of zolpidem should be used, which should not exceed 10 mg.

Elderly
Elderly or weaker patients may be especially sensitive to the effect of drug. Recommended dose is 5 mg.
Dosage may be increased to 10mg only where the clinical response is inadequate and drug is well tolerated.

Patients with hepatic impairment
In patients with hepatic impairment, clearance and metabolism of drug is not as fast as in healthy individuals. Therefore, in these patients, the recommended starting dose is 5mg. Only in the case that the effect is not sufficient and/or the patient tolerates medication well, dosage may be increased to 10mg. The maximum daily dose is 10mg and cannot be exceeded

Children and adolescents under 18
The safety and efficacy of zolpidem in children and adolescents below 18 years has not been proven, therefore it is not allowed its use in this population.

4.3. Contraindications

- ZASAN (zolpidem) is contraindicated in patients with a hypersensitivity to zolpidem or any of the excipients.

- ZASAN is contraindicated in patients with obstructive sleep apnea, myasthenia gravis, severe hepatic insufficiency, acute and/or severe respiratory depression.

- In absence of data, ZASAN tablets should not be prescribed for children or patients with psychotic illness.

4.4. Special warnings and precautions for use

Sleep disorders can be symptoms of physical and / or mental disorder, according to the findings observed during treatment with sedatives / hypnotics, including treatment with ZASAN tablets. Since significant side effects of Zasan tablets appears to be dose dependent, it is important to take the lowest effective dose, especially with the elderly.
Symptomatic treatment of insomnia should be initiated only after a careful assessment of the patient's condition, i.e. indentifying and treating underlying disorders. If insomnia is present after 7-10 days of treatment, it is necessary to check whether there might be a primary psychiatric or physical disorder. Worsening of insomnia or the emergence of new disorder of thoughts or behavior are possible consequences of unrecognized mental or physical disorders.
Because of depressive effect on the central nervous system and rapid onset of action, zolpidem should be taken just before bedtime. Patients should be able to sleep undisturbed for 7-8 hours after taking the medication.
To elderly or weaker patients should be prescribed a lower dose (see 4.2.). Because of myorelaxant effect of zolpidem, especially in elderly patients there is increased risk of falls and consequently hip fractures.
There is a little clinical experience in the use of Zasan tablets in patients who at same time suffer from some systemic disease. Caution is required in patients with diseases (conditions) that may affect the metabolism or hemodynamics. Although clinical trials have not shown that in therapeutic dose Zasan tablets cause respiratory depression, caution is needed if Zasan tablets are administered to patients with impaired respiratory function, as sedative hypnotics may cause respiratory depression (see 4.3.).

Depression
As with other hypnotic drug, Zasan should be administered with caution in patients exhibiting symptoms of depression. Suicidal tendencies may be present therefore the minimum effective dose of Zasan tablets should be prescribed to these patients to avoid the possibility of intentional overdosage by the patient. Pre-existing depression may be unmasked during use of Zasan tablets. Since insomnia may be a symptom of depression, the patient should be re-evaluated if insomnia persists.

Extreme caution should be exercised when prescribing for patients with a history of drug or alcohol abuse. These patients should be under careful surveillance, since they are at risk of habituation and phychological dependence.

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

Dependence
Use of benzodiazepines or benzodiazepine-like agents may lead to the development of physical and psychological dependence. The risk of dependence increases with dose and duration of treatment. The risk is also greater in patients with a history of psychiatric disorders and / or drug abuse. These patients should be under careful surveillance when receiving hypnotics.
Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. It may consist of headaches or muscle pain, extreme anxiety and tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealisation, depersonalization, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, nose and physical contact, hallucinations and epileptic seizures.

Rebound insomnia
Transient syndrome is characterized with recurrence of symptoms that lead to treatment with benzodiazepine or related preparations,in an enhanced form,and symptoms may occur after discontinuation of treatment with hypnotic.. It may be accompanied by other reactions including mood changes, anxiety and restlessness.
It is important that patient be aware of possibly feedback insomnia, thus his anxiety with the onset of these symptoms after the drug is discontinued decreases on slightest possible. Since the risk of withdrawal or rebound phenomena has been shown to be greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually where it is clinically appropriate. There are indications that, in the case of benzodiazepines and benzodiazepine-like products with the short activity, withdrawal phenomen can become manifest within the dosage interval, especially when the dosage is high.

Amnesia
Benzodiazepines or benzodiazepine-like agents may induce anterograde amnesia. The condition usually occurs several hours after ingesting the product and in order to reduce the risk, patients should be sure that they will be able to sleep undisturbed 7 to 8 hours.

Other psychiatric and “paradoxical” reactions
Other reactions like restlessness, exacerbated insomnia, agitation, irritability, aggression, delusion, anger, nightmares, hallucinations, psychosis, abnormal behavior and other adverse behavioral effects are known to occur when using benzodiazepines or benzodiazepine-like agents. If this reactions occur, use of the product should be discontinued. These reactions are more likely to occur in the elderly.
Somnambulism
Sleepwalking and other associated forms of behavior such as "driving in a dream", preparing and eating food, making phone calls, or having sex, with amnesia for the event, have been described in patients who have used Zasan and were not fully awake.The use of alcohol and other CNS-depressant with Zasan tablets appears to increase the risk of such behaviors, as does the use of Zasan at doses exceeding the maximum recommended dose. Discontinuation of Zasan should be strongly considered for patients who report such behaviors.

Duration of treatment
Treatment should be as short as possible. It should not be longer than 4 weeks, including the time for gradual reduction of the dose. If the treatment takes longer than recommended, it is necessary to re-evaluate the patient's condition. At the beginning of treatment may be useful to instruct patients on the length of treatment and explain in detail the process of gradually reducing the dose.
Other warnings
Because of lactose, patient with rare hereditary problems such as galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

General information about the effects of benzodiazepines and other hypnotics in which the doctor must pay attention when prescribing
Next-day psychomotor impairment
The risk of next-day psychomotor impairment, including impaired driving ability, is increased if:
 zolpidem is taken within less than 8 hours before performing activities that require mental alertness (see section 4.7)
  a dose higher than the recommended dose is taken
  zolpidem is co-administered with other CNS depressants or with other drugs that increase the blood levels of zolpidem, or with alcohol or illicit drugs (see sections 4.5)
Zolpidem should be taken in a single intake just before bedtime and not be re-administered during the same night.

4.5. Interaction with other medicinal products and other forms or 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.
Enhancement of the central depressive effect may occur in case of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, antiepileptic drugs, anaesthetics and sedative antihistamines.

In the case of narcotic analgesics enhancement of euphoria may also occur leading to an increase in psychological dependence.
Compounds that inhibit hepatic enzymes (particularly cytochrome P450) may enhance the activity related preparation.
ZASAN is metabolized by several cytochrome P450 liver enzymes, the main enzyme is CYP3A4 with the contribution of CYP1A2. Pharmacodynamic effect of Zasan tablets is reduced when administered with rifampicin (a CYP3A4 inducer). However, when Zasan is applied with itraconazole (a CYP3A4 inhibitor), that does not change significantly its pharmacokinetics and pharmacodynamics.
Since CYP3A4 plays a significant role in the metabolism of Zasan tablets, there should be taken into account the possible interaction with drugs that reduce or enhance the activity of CYP3A4. Co-administration of ciprofloxacin may increase blood levels of zolpidem, therefore concurrent use is not recommended.
Due to concomitant administration of ketoconazole, excretion was slow (probably due to decreased metabolism) and plasma levels of zolpidem were elevated with subsequent amplification pharmacodynamic effects of zolpidem.
Ritonavir has a similar effect on the kinetics of zolpidem. When concomitant administration of ritonavir there may be increased the risk of excessive sedation and respiratory depression.

When ZASAN tablets were administered with ranitidine or cimetidine, no significant pharmacokinetics interactions were observed.

4.6. Pregnancy and lactation

Animal studies have shown no teratogenic or embryotoxic effects. Drug effects on pregnancy are not sufficiently tested and it is therefore recommended to avoid using during pregnancy, especially during the first three months.
If the product is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuance of the product if she intends to become or suspect that she is pregnant.
If, for compelling medical reason, ZASAN is administered during the late phase of pregnancy, or during labor, effects on the neonate, such as hypothermia, hypotonia and moderate respiratory depression, can be expected due to the pharmacological action of the product.

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

Small amounts of ZASAN tablets can be found in breast milk, and therefore is not recommended its use in nursing mothers.

4.7. Effects on ability to drive and use machines

▲ Trigonic, a drug with strong influence on psycho-physical abilities. During therapy it is forbidden to operate motor vehicles or machines, if it is not passed at least 12 hours of use of the drug!

4.8. Undesirable effects

There are evidence suggesting that the side effects,especially some occuring on CNS and gastrointestinal system during ZASAN drug use are dose-dependent. It is recommended that the drug is taken just prior rest and sleep time so side effects will be less.. Adverse effects are more common in older patients.

Adverse reactions are classified according to frequency:
Very common (≥1/10),
Common(≥1/100 i <1/10),
Uncommon (≥1/1000 i <1/100),
Rare (≥1/10000 i <1/1000),
Very rare (<1/10000),

Not known (cannot be estimated based on available data)

Metabolism and nutrition disorders
Uncommon: hypoglycemia

Gastro-intestinal Disorders
Common: diarrhea
Uncommon: nausea, vomiting, constipation, dysphagia, flatulence, hiccups, gastroenteritis.

General disorders and administration side conditions
Common: fatigue
Uncommon: nausea, impaired walking, edema, fever (especially in elderly patients and when the drug is not used in accordance with the recommendations).

Musculoskeletal and connective tissue disorders
Uncommon: muscular weakness, arthritis

Renal and urinary system disorders
Uncommon: cystitis, incontinence

Poremećaji nervnog sistema
Common: daytime sleepiness, emotional lability, somnolence, headache, faintness, worsening or insomnia, dizziness, ataxia, anterograde amnesia, which may be accompanied by inappropriate behavior
Uncommon: migraine, paraesthesia, tremor, stupor, decreased level of consciousness, trouble concentrating

Cardiac disorders
Uncommon: tachicardia

Vascular disorders
Uncommon: cerebrovascular disorders, hypertension, hypotension, orthostatic hypotension

Respiratory, thoracic and mediastinal disorders
Uncommon: bronchitis, cough, dyspnoea

Eye disorders
Uncommon: diplopia

Psychiatric disorders
Common: hallucination, agitation, nightmare
Uncommon: confusional state, irritability, euphoria, restlessness
Rare: aggression, delusion, psychosis, somnabulism, abnormal behavior (often observed in the elderly (see 4.4.), libido disorders
Most of these psychiatric undesirable effects are related to paradoxical reactions
Very rare: anger
Symptoms of depression may be expressed during treatment with benzodiazepines and benzodiazepine-like agents (see 4.4.).
The use of zolpidem (even therapeutic doses) can cause the development of physical and psychological dependence; discontinuation of treatment may cause withdrawal symptoms or rebound of insomnia. It was recorded abuse in people with addictions.

Skin and subcutaneous tissue disorders
Uncommon: rash, pruritus, increased sweating
Rare: pallor, angioedema

Immune system disorders
Unknown angioneurotic edema

Reproductive system and breast disorders
Uncommon: menstrual disorders, vaginitis

Injury, poisoning and procedural complications
Uncommon: falls, trauma.

Hapatobiliary disorders
Rare: elevated liver enzymes (ALT)

4.9. Overdose

Research on overdose with ZASAN tablets with or without other drugs with CNS depressant (including alcohol), consciousness disturbance varied from somnolence to coma, including fatal outcomes.

General symptomatic and supportive measures should be used in case of overdose. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Sedative drugs should be withheld even if excitation occurs. Use of flumazenil may be considered when serious symptoms are observed, who has a half life around 40-80 minutes. Patient should be closely monitored due to the short –acting of flumazenil, and additional doses may be necessary, but it should be emphasized that the use of flumazenil may contribute to the occurrence of neurological symptoms (convulsions).

The value of dialysis in the treatment of overdosage has not been established. Using dialysis in patients with renal failure receiving therapeutic doses of ZASAN did not reduced drug levels.

In the treatment of any drug overdose, it is necessary to bear in mind that the patient may have used more drugs at the same time, which need to be well established prior any supportive measures, if possible.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: formulations that act on the nervours system, psycholeptics, hypnotics, drug related to benzodiazepines.
ATC: N05CF02

ZASAN is imidazopyridine which selectively binds to the je omega-1 subtype receptor (also known as a subtype of benzodiazepine 1) corresponding to the $GABA_A$ receptors containing the alpha subtype of -1, whereas benzodiazepines non-selectively bind both with omega 1 and omega 2 subtypes. The effect on chloride ions channels via this receptor is realized the specific sedative effects of the drug ZASAN. These effects are withdrawn with acting benzodiazepine antagonist, flumazenil.

The drug in treatment of animals: the selective binding of the drug to ZASAN omega-1 receptors may explain the apparent lack of anticonvulsant effects and the effects on muscle relaxation in hypnotic dose in animals that commonly occur with benzodiazepines which are not selective for omega-1 receptors.

Administration of drug in treatment of people: ZASAN increases the stability of sleep and reduces the number of awakening and prolongs sleep duration and quality of sleep. This effect is associated with a characteristic EEG profile, which differs from the benzodiazepines. Trials that measured the percentage of time spent in each sleep stage, Zasan has generally proved to maintain sleep stages. When using the recommended dose of ZASAN has no effect on the duration of paradoxical sleep (REM). The preservation of deep sleep (stage 3 and 4 slow-wave sleep) may be explained by a selective binding of the omega-1 receptors. All described effects of ZASAN drug are withdrawn with acting benzodiazepine antagonist, flumazenil.

5.2. Pharmacokinetic properties

ZASAN has both, a rapid absorption and onset of hypnotic effect. Bioavailability is to 70% following oral administration, and it demonstrates linear kinetics in the therapeutic dose range. Peak plasma concentration is reached at between 0.5 and 3 hours after administration

The elimination half-life of ZASAN drug is short, with a mean value of 2,4 hours (±0,2 h), and duration of action is up to 6 hours.
Protein binding amounts to 92,5% ± 0,1%. First past metabolism by the liver amounts to approximately 35%. Repeated use of the drug did not affect protein binding, proving the lack of competition at the binding sites between Zasan drug and its metabolites.

5.3. Preclinical safety data

For oral administration in dosages of 40-100 mg/kg per day ZASAN did not affect the fertility of male and female rats and only in exceptional cases recorded irregular oestrus cycles and prolonged pre-coitus period.
In young pregnant females rats' high dosage of ZASAN (20-100 mg/kg) caused the ataxia and lethargy and incomplete cranial bone ossification of the fetus. Such effects are frequently observed in rats treated with sedatives and hypnotics.
After drug administration teratogenic effects have not been reported.The dose of 4 mg/kg did not cause toxicity in females and fetuses. At a dose of 16mg /kg in a pregnant female rabbits there have been observed increased post-implatation fetal loss and incomplete ossification in living fetuses. These fetal changes are attributed to the reduced weight in females. Teratogenic effects are not noticed .

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

ZASAN 5 mg

- Microcrystalline cellulose,
- Lactose monohydrate,
- Copovidone,
- Sodium starch glycolate,
- Talc,
- Magnesium stearate

Film: Opadry II pink, purified water

ZASAN 10 mg

- Microcrystalline cellulose,
- Lactose monohydrate,
- Copovidone,
- Sodium starch glycolate,
- Talc,
- Magnesium stearate

Film: Opadry II pink, purified water

6.2. Incompatibilities

None known.

6.3. Shelf life

2 years.

6.4. Special precautions for storage

ZASAN film tablets store up to 25°C in original packaging, out of reach of children!
There are no special requirements of storage.

6.5. Nature and contents of container

Carton box with 20 film-coated tablets of 5 mg of zolpidem in a blister pack (2 blisters x 10 tablets)
Carton box with 20 film-coated tablets of 10 mg of zolpidem in a blister pack (2 blisters x 10 tablets)

6.6. Special precautions for disposal

The processing of unused drugs and waste materials obtained from these drugs is carried out according to the regulation for the handling and disposal of pharmaceutical waste.

7. MARKETING AUTHORISATION HOLDER

ZADA Pharmaceuticals Ltd.,
Donji Bistarac,
75300 Lukavac,
Bosnia and Herzegovina.

8. MARKETING AUTHORISATION NUMBER

▲ ZASAN film tablets 5 mg: 04-07.3-2-2410/16
▲ ZASAN film tablets 10 mg: 04-07.3-2-2411/16

9. DATE AND NUMBER OF RENEWAL OF THE AUTHORISATION

▲ ZASAN film tablets 5 mg: 07.03.2017.
▲ ZASAN film tablets 10 mg: 07.03.2017.