**SCHEDULING STATUS**
S5

## 1. NAME OF THE MEDICINE
**ZOLPIDEM XR 12,5 ADCO**, extended-release tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION
ZOLPIDEM XR 12,5 ADCO: Each tablet contains 12,5 mg zolpidem tartrate.

Contains sugar (ZOLPIDEM XR 12,5 ADCO contains 120,85 mg lactose monohydrate per tablet).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM
Extended-release tablets.
ZOLPIDEM XR 12,5 ADCO: Blue coloured, round, biconvex, film-coated tablets debossed with E62 on one side and LU on the other side.

## 4. CLINICAL PARTICULARS
### 4.1 Therapeutic indications
Short-term treatment of insomnia.
ZOLPIDEM XR 12,5 ADCO is indicated in adults below the age of 65 years, and only when the disorder is severe, disabling or subjecting the individual to extreme distress.

### 4.2 Posology and method of administration
**Posology**
ZOLPIDEM XR 12,5 ADCO acts rapidly and therefore should be taken immediately before bedtime, or in bed.
For a faster sleep onset, ZOLPIDEM XR 12,5 ADCO should not be administered with or immediately after a meal (see section 5.2).
ZOLPIDEM XR 12,5 ADCO should be taken in a single intake and not be re-administered during the same night.

Treatment should be as short as possible. Generally, the duration of treatment varies from four days to two weeks with a maximum, including the tapering off process, of four weeks. In certain cases, extension beyond the maximum treatment period may be necessary; if so, it should not take place without re-evaluation of the patient's status.
Treatment should be started with the lowest recommended dose. The maximum dose should not be exceeded.

***Adults (< 65* years*):***
The recommended daily dose is 12,5 mg.

The lowest effective daily dose of ZOLPIDEM XR 12,5 ADCO should be used and must not exceed 12,5 mg.

**Special populations**

***Hepatic impairment:***

ZOLPIDEM XR 12,5 ADCO should not be used in patients with severe hepatic impairment (see sections 4.3. and 4.4).

***Renal impairment:***

No dosage adjustment is required.

***Elderly patients:***

As ZOLPIDEM XR 12,5 ADCO has not been evaluated in elderly patients (≥ 65 years), ZOLPIDEM XR 12,5 ADCO is not recommended in this population.

***Children:***

Safety and effectiveness of ZOLPIDEM XR 12,5 ADCO in paediatric patients under the age of 18 years have not been established. Therefore, ZOLPIDEM XR 12,5 ADCO should not be prescribed in this population (see section 4.3).

**Method of administration**

Oral administration.

Tablets should not be halved, crushed or chewed.

**4.3 Contraindications**

- Hypersensitivity to the active substance zolpidem tartrate or any of the excipients listed in section 6.1.
- Children under the age of 18 years.
- Sleep apnoea syndrome.
- Myasthenia gravis.
- Severe hepatic impairment.
- Acute and/or severe respiratory impairment.
- Pregnancy and lactation (see section 4.6).

**4.4 Special warnings and precautions for use**

General information related to effects seen following administration of hypnotics, which should be considered by the prescribing medical practitioner are described below.

The cause of insomnia should be identified wherever possible and the underlying factors treated before a hypnotic is prescribed.

The failure of insomnia to remit after a 7 – 14-day course of treatment may indicate the presence of a primary psychiatric or physical disorder, and the patient should be carefully re-evaluated at regular intervals.

**Respiratory impairment**
Hypnotics have the capacity to depress respiratory drive, precautions should be observed if ZOLPIDEM XR 12,5 ADCO is prescribed to patients with mild to moderate compromised respiratory function.

**Risks from concomitant use with opioids**
Concomitant use of opioids with benzodiazepines or other sedative-hypnotic medicines, including ZOLPIDEM XR 12,5 ADCO, may result in sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of opioids and benzodiazepines for use in patients for whom alternative treatment options are inadequate.
If a decision is made to prescribe ZOLPIDEM XR 12,5 ADCO concomitantly with opioids, prescribe the lowest effective dosages and minimum duration of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation.

**Amnesia**
ZOLPIDEM XR 12,5 ADCO may induce anterograde amnesia. The condition occurs most often several hours after ingesting ZOLPIDEM XR 12,5 ADCO and therefore, to reduce the risk, patients should ensure that they get a full night's sleep (7 – 8 hours) before being active.

**Other psychiatric and paradoxical reactions**
Other psychiatric and paradoxical reactions like restlessness, exacerbated insomnia, agitation, irritability, aggression, delusion, anger, nightmares, hallucinations, abnormal behaviour and other behavioural effects are known to occur when using ZOLPIDEM XR 12,5 ADCO. Should this occur, use of ZOLPIDEM XR 12,5 ADCO should be discontinued. These reactions are more likely to occur in the elderly.

**Somnambulism and associated behaviours**
Sleep walking and other associated behaviours such as "sleep driving", preparing and eating food, making phone calls or having sex, with amnesia for the event have been reported in patients who have taken ZOLPIDEM XR 12,5 ADCO and were not fully awake. The use of alcohol and other central nervous system (CNS) depressants with ZOLPIDEM XR 12,5 ADCO appears to increase the risk of such behaviours, as does the use of ZOLPIDEM XR 12,5 ADCO at doses exceeding the maximum recommended dose. Discontinuation of ZOLPIDEM XR 12,5 ADCO should be strongly considered for patients who report such behaviours.

**Psychomotor impairment**
The risk of psychomotor impairment, including impaired driving ability, is increased if: ZOLPIDEM XR 12,5 ADCO is taken within less than 7 – 8 hours before performing activities that require mental alertness, a dose higher than the recommended dose is taken, or ZOLPIDEM XR 12,5 ADCO is co- administered with other CNS depressants, alcohol, or with other medicines that increase the blood levels of ZOLPIDEM XR 12,5 ADCO.

**Tolerance**
Some loss of efficacy to the hypnotic effects of ZOLPIDEM XR 12,5 ADCO may develop after repeated use for a few weeks.

**Dependence**
Use of ZOLPIDEM XR 12,5 ADCO may lead to the development of physical and psychological dependence. The risk of dependence increases with dose and duration of treatment. It is also greater in patients with a history of psychiatric disorders and/or alcohol or medicine abuse. Patients with a history of psychiatric disorders should be under careful surveillance when receiving ZOLPIDEM XR 12,5 ADCO.
Patients with a history of alcohol or medicine abuse (see Patients with a history of alcohol and medicine abuse).
Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches or muscle pain, extreme anxiety and tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.
Dependence has been reported with ZOLPIDEM XR 12,5 ADCO (see section 4.8).

**Rebound insomnia**
A transient syndrome, whereby the symptoms that led to treatment with ZOLPIDEM XR 12,5 ADCO recur in an enhanced form, may occur on withdrawal of ZOLPIDEM XR 12,5 ADCO treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness. There are indications that, in the case of ZOLPIDEM XR 12,5 ADCO with a short duration of action, withdrawal phenomenon can become manifest within the dosage interval, especially when the dosage is high.
The rebound phenomenon, if it occurs with ZOLPIDEM XR 12,5 ADCO, was limited to the first night after the medicine discontinuation.
It is important that the patient should be aware of the possibility of rebound phenomenon, thereby minimising anxiety over such symptoms should they occur when the ZOLPIDEM XR 12,5 ADCO is discontinued.

**Patients with a history of alcohol or medicine abuse**
ZOLPIDEM XR 12,5 ADCO should not be used in patients with a history of alcohol or medicine abuse.

**Hepatic impairment**
ZOLPIDEM XR 12,5 ADCO should be used with caution in patients with mild to moderate hepatic impairment. ZOLPIDEM XR 12,5 ADCO must not be used in patients with severe hepatic impairment as it may contribute to encephalopathy (see sections 4.3 and 5.2).
**Psychotic illness**
ZOLPIDEM XR 12,5 ADCO is not recommended for the primary treatment of psychotic illness.

**Suicidality and depression**
Several epidemiological studies show an increased incidence of suicide and suicide attempt in patients with or without depression, treated with benzodiazepines and other hypnotics, including ZOLPIDEM XR 12,5 ADCO. A causal relationship has not been established.
ZOLPIDEM XR 12,5 ADCO should not be used alone to treat depression or anxiety associated with depression (suicide may be precipitated in such patients). As suicidal tendencies may be present, the least amount of ZOLPIDEM XR 12,5 ADCO that is feasible, should be supplied to these patients because of the possibility of intentional over dosage by the patient. A pre-existing depression may be unmasked during the use of ZOLPIDEM XR 12,5 ADCO. Since insomnia may be a symptom of depression, the patient should be re-evaluated if insomnia persists.

**Severe injuries**
Due to its pharmacological properties, ZOLPIDEM XR 12,5 ADCO can cause drowsiness and a decreased level of consciousness, which may lead to falls and consequently to severe injuries.

**Patients with long QT syndrome**
An *in vitro* cardiac electrophysiological study showed that under experimental conditions using very high concentration and pluripotent stem cells, ZOLPIDEM XR 12,5 ADCO may reduce the hERG (human ether-a-go-go-related gene) related potassium currents. The potential consequence in patients with congenital long QT syndrome is unknown. As a precaution, the benefit/risk ratio of ZOLPIDEM XR 12,5 ADCO treatment in patients with known congenital long QT syndrome should be carefully considered.

**Lactose intolerance**
ZOLPIDEM XR 12,5 ADCO contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take ZOLPIDEM XR 12,5 ADCO.

**Contains sodium**
This medicine contains less than 1 mmol sodium (23 mg) per extended-release tablet, that is to say essentially ‘sodium-free’.

**4.5 Interaction with other medicines and other forms of interaction**
**Alcohol**
Concomitant use with alcohol is not recommended. The sedative effect may be enhanced when ZOLPIDEM XR 12,5 ADCO is used in combination with alcohol. This affects the ability to drive or use machines.

**CNS depressants**
Enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant medicines, narcotic analgesics, antiepileptic medicines, anaesthetics and sedative antihistamines. Concomitant use of ZOLPIDEM XR 12,5 ADCO with these medicines may increase drowsiness and psychomotor impairment, including impaired driving ability.

Concomitant use with hypnotics may enhance the euphoric effect of narcotic analgesics, which may lead to an increase in psychological dependence.
Co-administration of fluvoxamine may increase blood levels of ZOLPIDEM XR 12,5 ADCO; concurrent use is not recommended (see CYP450 inhibitors and inducers).

**Opioids**
The concomitant use of benzodiazepines and other sedative-hypnotic medicines, including ZOLPIDEM XR 12,5 ADCO, and opioids increases the risk of sedation, respiratory depression, coma, and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4).

**CYP450 inhibitors and inducers**
Compounds which inhibit cytochrome P450 may enhance the activity of ZOLPIDEM XR 12,5 ADCO.
Co-administration of ZOLPIDEM XR 12,5 ADCO with ketoconazole (200 mg twice daily), a potent CYP3A4 inhibitor, produced a 64 % increase in ZOLPIDEM XR 12,5 ADCO plasma levels. A routine dosage adjustment of ZOLPIDEM XR 12,5 ADCO is not necessary, but patients should be advised that the sedative effects might be enhanced.
However, co-administration of ZOLPIDEM XR 12,5 ADCO with itraconazole or fluconazole did not produce any significant changes in ZOLPIDEM XR 12,5 ADCO pharmacokinetics and pharmacodynamics.
Fluvoxamine is a strong inhibitor of CYP1A2 and a moderate to weak inhibitor of CYP2C9 and CYP3A4. Co-administration of fluvoxamine may increase blood levels of ZOLPIDEM XR 12,5 ADCO; concurrent use is not recommended.
Ciprofloxacin has been shown to be a moderate inhibitor of CYP1A2 and CYP3A4. Co-administration of ciprofloxacin may increase blood levels of ZOLPIDEM XR 12,5 ADCO; concurrent use is not recommended.
The pharmacodynamic effect of ZOLPIDEM XR 12,5 ADCO is decreased when it is administered with a CYP3A4 inducer such as rifampicin due to an increase in liver metabolism.
The pharmacodynamics effect of ZOLPIDEM XR 12,5 ADCO is decreased when it is administered with a CYP3A4 inducer, such as St. John’s Wort. Co-administration of St. John’s Wort may decrease blood levels of ZOLPIDEM XR 12,5 ADCO; concurrent use is not recommended.

**Antiretrovirals**
HIV-protease inhibitors such as ritonavir may increase plasma concentrations of zolpidem with a risk of extreme sedation and respiratory depression; use together is possible provided the patient is carefully monitored for excessive sedative effects.

**Other**
No significant pharmacokinetic interactions were observed when ZOLPIDEM XR 12,5 ADCO was administered with warfarin, digoxin, ranitidine or cimetidine.

**4.6 Fertility, pregnancy and lactation**

**Women of childbearing potential**

If ZOLPIDEM XR 12,5 ADCO is prescribed to a woman of childbearing potential, she should be warned to contact her medical practitioner about stopping ZOLPIDEM XR 12,5 ADCO if she intends to become, or suspects that she is pregnant.

**Pregnancy**

Safety in pregnancy has not been established.

The use of ZOLPIDEM XR 12,5 ADCO during pregnancy should be avoided (see section 4.3).

If for compelling medical reasons ZOLPIDEM XR 12,5 ADCO is administered during the late phase of pregnancy or during labour, effects on the neonate, such as hypothermia, hypotonia and moderate respiratory depression, can be expected due to the pharmacological action of zolpidem.

Infants born to mothers who took hypnotics, including ZOLPIDEM XR 12,5 ADCO, chronically during the latter stages of pregnancy may have developed physical dependence and may be at risk of developing withdrawal symptoms in the postnatal period.

**Breastfeeding**

As zolpidem is excreted in breast milk, the use of ZOLPIDEM XR 12,5 ADCO in breastfeeding mothers should be avoided (see section 4.3).

**Fertility**

There is no data on fertility.

**4.7 Effects on ability to drive and use machines**

Patients should be warned that there may be a possible risk of adverse reactions including drowsiness, prolonged reaction time, dizziness, sleepiness, blurred/double vision, and reduced alertness and impaired driving the morning after therapy.

In order to minimise this risk, a full night of sleep (7 – 8 hours) is recommended. Furthermore, the co-administration of ZOLPIDEM XR 12,5 ADCO with alcohol and other CNS depressants increases the risk of such effects. Patients should be warned not to use alcohol or other psychoactive substances when taking ZOLPIDEM XR 12,5 ADCO (see sections 4.4. and 4.5).

**4.8 Undesirable effects**

**a) Summary of the safety profile**

The reaction most commonly associated with discontinuation in a 3-week study was somnolence, whilst in a 6-month study, anxiety, restlessness or agitation, (depression, major depression or depressed mood) were the most common adverse effects that resulted after discontinuation of treatment.

Short-term studies indicate the most common adverse effects to be headache, next-day somnolence and dizziness. A six month study revealed the most common adverse effects to be the same as those indicated in short-term use, with the addition of higher incidence of anxiety.

There is evidence of a dose-relationship for adverse effects associated with ZOLPIDEM XR 12,5 ADCO use, particularly for certain CNS events. They occur most frequently in elderly patients.

**b) Tabulated list of adverse reactions**

| System Organ Class | Frequency | Side effects |
|---|---|---|
| Infections and infestations | Frequent | Influenza |
| | Less frequent | Gastroenteritis, labyrinthitis, lower respiratory tract infection, otitis externa, upper, respiratory tract infection |
| Blood and lymphatic system disorders | Less frequent | Anaemia, hyperhaemoglobinaemia, leukopenia, lymphadenopathy, macrocytic anaemia, thrombosis |
| Immune system disorders | Less frequent | Infection, abscess, herpes simplex zoster, otitis externa, otitis media, allergic reaction, allergy aggravated, anaphylactic shock |
| | Frequency unknown | Angioedema |
| Metabolism and nutrition disorders | Less frequent | Appetite disorder, hyperglycaemia, thirst, gout, hyperlipidaemia, increased alkaline phosphatase, increased BUN, periorbital oedema, appetite increased, weight decreased |
| Psychiatric disorders | Frequent | Anxiety, psychomotor retardation, disorientation |
| | Less frequent | Depression, hallucination, apathy, binge eating, confusional state, depersonalisation, depressed mood, disinhibition, euphoric mood, hallucination, including visual and hypnagogic hallucination, mood swings, nightmares, stress symptoms |
| | Frequency unknown | Sleep walking, restlessness, aggression, delusion, anger, abnormal behaviour (see section 4.4), dependence (withdrawal symptoms, or rebound effects may occur after treatment discontinuation) |
| Nervous system disorders | Frequent | Headache, somnolence, dizziness, cognitive disorders such as memory disorders (memory impairment, amnesia, anterograde amnesia), disturbance in attention, drugged feeling, euphoria, insomnia, lethargy, light-headedness, dry mouth |
| | Less frequent | Balance disorder, hypoesthesia, paraesthesia, ataxia, burning sensation, |

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| | | postural dizziness, dysgeusia, involuntary muscle contractions, tremor, agitation, decreased cognition, detached, difficulty concentrating, dysarthria, emotional liability, illusion, leg cramps, migraine, nervousness, sleeping (after daytime dosing), speech disorder, stupor, abnormal gait, abnormal thinking, aggressive reaction, apathy, decreased libido, delusion, dementia, depersonalisation, neuralgia, neuritis, neuropathy, neurosis, panic attacks, paresis, personality disorder, somnambulism, suicide attempts, tetany, yawning, increased swelling, pallor, syncope, altered saliva, flushing, impotence, increased saliva, tenesmus |
| Eye disorders | Frequent | Visual disturbance, diplopia, eye redness, vision blurred |
| | Less frequent | Altered visual depth perception, asthenopia, eye irritation, eye pain, scleritis, conjunctivitis, corneal ulceration, abnormal lacrimation, photopsia, abnormal accommodation, glaucoma |
| Ear and labyrinth disorders | Less frequent | Vertigo, tinnitus |
| Cardiac disorders | Less frequent | Palpitations, tachycardia, angina pectoris, dysrhythmia, circulatory failure, extrasystoles, myocardial infarction, pulmonary embolism, pulmonary oedema, ventricular tachycardia |
| Vascular disorders | Less frequent | Postural hypotension, hypotension, cerebrovascular disorder, hypertension, arteritis, hypertension aggravated, phlebitis, varicose veins |
| Respiratory, thoracic and mediastinal disorders | Frequent | Sinusitis |
| | Less frequent | Cough, dry throat, throat irritation, bronchitis, dyspnoea, bronchospasm, respiratory depression epistaxis, hypoxia, laryngitis, pneumonia |
| Gastrointestinal disorders | Frequent | Nausea, constipation, diarrhoea, dyspepsia, hiccup |
| | Less frequent | Vomiting, abdominal discomfort, flatulence, frequent bowel movements, gastroesophageal reflux disease, enteritis, |

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|---|---|---|
| | | eructation, gastritis, haemorrhoids, intestinal obstruction, rectal haemorrhage, tooth caries |
| Blood and lymphatic disorder | Less frequent | Anaemia, hyperhaemoglobinaemia, leukopenia, lymphadenopathy, macrocytic anaemia, purpura, porphyria |
| Hepatobiliary disorders | Frequency unknown | Hepatocellular, cholestatic or mixed liver injury |
| Skin and subcutaneous tissue disorders | Less frequent | Rash, urticaria, contact dermatitis, skin wrinkling, pruritus, acne, bullous eruption, furunculosis |
| Musculoskeletal, connective tissue and bone disorders | Frequent | Myalgia, muscle cramp, neck pain, back pain |
| | Less frequent | Arthralgia, arthritis, arthrosis, sciatica, tendonitis |
| | Frequency unknown | Muscle weakness |
| Renal and urinary disorders | Frequent | Urinary tract infection |
| | Less frequent | Dysuria, cystitis, urinary incontinence, acute renal failure, micturition frequency, nocturia, polyuria, pyelonephritis, renal pain, urinary retention |
| Reproductive system and breast disorders | Less frequent | Dysmenorrhoea, menorrhagia, vulvovaginal dryness, menstrual disorder, vaginitis, breast fibroadenosis, breast neoplasm, breast pain |
| General disorders and administrative site conditions | Frequent | Fatigue |
| | Less frequent | Asthenia, chest discomfort, feeling drunk, influenza-like illness, lethargy, pain, oedema, falling, pyrexia, malaise, trauma, face oedema, hot flashes, restless legs, rigors, tolerance increased, medicine tolerance |
| Investigations | Less frequent | Increased body temperature, heart rate increased, increased ESR |

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

### 4.9 Overdose

**Signs and symptoms**

In cases of overdose involving ZOLPIDEM XR 12,5 ADCO alone or with other CNS-depressant medicines (including alcohol), impairment of consciousness up to coma, and more severe symptomatology, including fatal outcomes have been reported.

**Management**

General symptomatic and supportive measures should be used. Activated charcoal should be given to reduce absorption. Sedating medicines should be withheld even if excitation occurs. Use of flumazenil may be considered where serious symptoms are observed. However, flumazenil administration may contribute to the appearance of neurological symptoms (convulsions).
ZOLPIDEM XR 12,5 ADCO is not dialysable.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Category and class: A 2.2 Sedatives, hypnotics
Pharmacotherapeutic group: Nervous system, Psycholeptics, Hypnotics and sedatives, Benzodiazepine related drugs
ATC code: N05CF02

Zolpidem is a benzodiazepine receptor agonist. Benzodiazepine receptor agonists (BZRAs) exert their pharmacological effects by binding to a site associated with GABA-A receptors. Zolpidem shows selectivity for a subtype of GABA-A receptors containing alpha-1 subunits. Scientific evidence suggests that this receptor subtype mediates drug-induced sedative/hypnotic effects.

### 5.2 Pharmacokinetic properties

**Absorption**

After oral intake, the absolute bioavailability is around 70 % and the peak plasma concentration is reached between 1,5 and 2,5 hours. The inter-individual variability (CV) is around 40 – 60 % for AUC and 30 – 40 % for $C_{max}$.
The elimination $t_{½}$ is 2,8 hours in healthy volunteers.
When zolpidem is administered after food, $C_{max}$ and AUC are decreased by 30 % and 23 % respectively and the time to maximal plasma concentration is delayed by 2 hours.

**Distribution**

The *in vitro* plasma protein binding is around 92 %. The distribution volume in adults is 0,54 L/kg following intravenous administration.

**Biotransformation**

Zolpidem is mainly metabolised by the hepatic cytochrome P450 CYP3A4
(around 60 % of the net CYP-mediated hepatic clearance). Other P450 isozymes such as CYP2C9, CYP1A2, CYP2D6 and CYP2C19 also contribute to the oxidation of the medicine. All

of zolpidem's metabolites are pharmacologically inactive. Zolpidem itself is not a significant inhibitor or inducer of human CYP isoforms.

**Elimination**
Zolpidem is excreted in the form of inactive metabolites in urine (around 60 %) and faeces (around 40 %). Clearance is around 212 mL/min. Reduced clearance of 100 mL/min has been noticed in the elderly.
Zolpidem plasma concentrations were measured approximately 9 hours post-dose on day 1 and day 15 in adult patients who were treated for 3 weeks with zolpidem 12,5 mg. Zolpidem concentrations did not change upon repeated dosing indicating no evidence of accumulation with zolpidem.

**Special populations**
***Hepatic impairment:***
In patients with liver impairment, the clearance of zolpidem is decreased and the elimination half-life is extended (around 10 hours) (see sections 4.2 and 4.4). In liver cirrhosis a 5-fold increase of AUC and a 3-fold increase of half-life have been observed.

***Renal impairment:***
In patients with renal impairment, whether dialysed or not, there is a moderate increase (around 30 %) of the volume of distribution compared to healthy subjects. Other pharmacokinetic parameters, such as clearance, AUC and elimination half-life are not affected. Therefore, no dose adjustment is necessary in patients with renal impairment.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

**Tablet core**
Colloidal silicon dioxide
FD & C Blue no. 2 aluminium lake (E132)
Hypromellose
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose
Potassium bitartrate
Sodium starch glycolate

**Coating**
ZOLPIDEM XR 12,5 ADCO: Opadry Blue (consisting of FD & C Blue no. 2 aluminium lake (E132), hypromellose, polyethylene glycol, titanium dioxide (E171)).

### 6.2 Incompatibilities

Not applicable

**6.3 Shelf life**
24 months.
Store at or below 30 °C.

**6.4 Special precautions for storage**
Keep the tablets in the bottle and the blister strip in the outer carton until required for use.

**6.5 Nature and contents of container**
Round, opaque white HDPE bottle with a child resistant closure containing a 1 g silica gel sachet.
Pack sizes: 30 or 100 tablets.

Clear PVC/Aclar film and plain aluminium foil (one side bright and other side dull and lacquered) blister strips, placed in an outer carton.
Pack sizes: 20 tablets (2 blister strips; 10 tablets per blister) or 30 tablets (3 blister strips; 10 tablets per blister)
Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**
No special requirements.

**7. HOLDER OF CERTIFICATE OF REGISTRATION**
Adcock Ingram Limited
1 New Road
Erand Gardens
Midrand, 1685
Customer Care: 0860 ADCOCK / 232625

**8. REGISTRATION NUMBER(S)**
57/2.2/0188

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
21 January 2025

**10. DATE OF REVISION OF THE TEXT**
20 August 2025