1. Name of the medicinal product

Zolyca75 mg capsules, hard

2. Qualitative and quantitative composition

Each capsule, hard contains 75 mg of Zolyca.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Capsule, hard.

Orange cap/white body, size “4” hard gelatin capsule shells, imprinted with 'Z' on cap and '12' on body with black ink contains white to off-white granular powder.

4. Clinical particulars

4.1 Therapeutic indications

Neuropathic pain

Zolyca is indicated for the treatment of peripheral and central neuropathic pain in adults.

Epilepsy

Zolyca is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

Generalised Anxiety Disorder

Zolycais indicated for the treatment of Generalised Anxiety Disorder (GAD) in adults.

4.2 Posology and method of administration

Posology

The dose range is 150 to 600 mg per day given in either two or three divided doses.

Neuropathic pain

Zolyca treatment can be started at a dose of 150 mg per day given as two or three divided doses. Based on individual patient response and tolerability, the dose may be increased to 300 mg per day after an interval of 3 to 7 days, and if needed, to a maximum dose of 600 mg per day after an additional 7-day interval.

Epilepsy

Zolyca treatment can be started with a dose of 150 mg per day given as two or three divided doses. Based on individual patient response and tolerability, the dose may be increased to 300 mg per day after 1 week. The maximum dose of 600 mg per day may be achieved after an additional week.

Generalised Anxiety Disorder

The dose range is 150 to 600 mg per day given as two or three divided doses. The need for treatment should be reassessed regularly.

Zolyca treatment can be started with a dose of 150 mg per day. Based on individual patient response and tolerability, the dose may be increased to 300 mg per day after 1 week. Following an additional week the dose may be increased to 450 mg per day. The maximum dose of 600 mg per day may be achieved after an additional week.

Discontinuation of Zolyca

In accordance with current clinical practice, if Zolyca has to be discontinued, it is recommended this should be done gradually over a minimum of 1 week independent of the indication (see sections 4.4 and 4.8).

Renal impairment

Zolyca is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. As Zolyca clearance is directly proportional to creatinine clearance (see section 5.2), dose reduction in patients with compromised renal function must be individualised according to creatinine clearance (CLcr), as indicated in Table 1 determined using the following formula:

$$CL_{cr}\,(ml/min) = \left(\frac{1.23 \times [140 - \text{age (years)}] \times \text{weight (kg)}}{\text{Serum creatinine (µmol/l)}} \right) (\times 0.85 \text{ for female patients})$$

Zolyca is removed effectively from plasma by haemodialysis (50% of drug in 4 hours). For patients receiving haemodialysis, the Zolyca daily dose should be adjusted based on renal function. In addition to the daily dose, a supplementary dose should be given immediately following every 4 hour haemodialysis treatment (see Table 1).

Table 1. Zolyca dose adjustment based on renal function

Creatinine Clearance (CLcr) (mL/min)	Total Zolyca daily dose *		Dose regimen
	Starting dose (mg/day)	Maximum dose (mg/day)	
≥ 60	150	600	BID or TID
≥30 - <60	75	300	BID or TID
≥15 - <30	25 – 50	150	Once Daily or BID
< 15	25	75	Once Daily
Supplementary dosage following haemodialysis (mg)			
	25	100	Single dose+

TID = Three divided doses

BID = Two divided doses

* Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose

+ Supplementary dose is a single additional dose

Hepatic impairment

No dose adjustment is required for patients with hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy of Zolyca in children below the age of 12 years and in adolescents (12-17 years of age) have not been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Elderly

Elderly patients may require a dose reduction of Zolyca due to a decreased renal function (see section 5.2).

Method of administration

Zolycamay be taken with or without food.

Zolycais for oral use only.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Diabetic patients

In accordance with current clinical practice, some diabetic patients who gain weight on Zolyca treatment may need to adjust hypoglycaemic medicinal products.

Hypersensitivity reactions

There have been reports in the postmarketing experience of hypersensitivity reactions, including cases of angioedema. Zolyca should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur.

Dizziness, somnolence, loss of consciousness, confusion and mental impairment

Zolyca treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. There have also been post-marketing reports of loss of consciousness, confusion and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicinal product.

Vision-related effects

In controlled trials, a higher proportion of patients treated with Zolyca reported blurred vision than did patients treated with placebo which resolved in a majority of cases with continued dosing. In the clinical studies where ophthalmologic testing was conducted, the incidence of visual acuity reduction and visual field changes was greater in Zolyca-treated patients than in placebo-treated patients; the incidence of fundoscopic changes was greater in placebo-treated patients (see section 5.1).

In the post-marketing experience, visual adverse reactions have also been reported, including loss of vision, visual blurring or other changes of visual acuity, many of which were transient.

Discontinuation of Zolyca may result in resolution or improvement of these visual symptoms.

Renal failure

Cases of renal failure have been reported and in some cases discontinuation of Zolyca did show reversibility of this adverse reaction.

Withdrawal of concomitant antiepileptic medicinal products

There are insufficient data for the withdrawal of concomitant antiepileptic medicinal products, once seizure control with Zolyca in the add-on situation has been reached, in order to reach monotherapy on Zolyca.

Withdrawal symptoms

After discontinuation of short-term and long-term treatment with Zolyca withdrawal symptoms have been observed in some patients. The following events have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, nervousness, depression, pain, convulsion, hyperhidrosis and dizziness, suggestive of physical dependence. The patient should be informed about this at the start of the treatment.

Convulsions, including status epilepticus and grand mal convulsions, may occur during Zolyca use or shortly after discontinuing Zolyca.

Concerning discontinuation of long-term treatment of Zolyca, data suggest that the incidence and severity of withdrawal symptoms may be dose-related.

Congestive heart failure

There have been post-marketing reports of congestive heart failure in some patients receiving Zolyca. These reactions are mostly seen in elderly cardiovascular compromised patients during Zolyca treatment for a neuropathic indication. Zolyca should be used with caution in these patients. Discontinuation of Zolyca may resolve the reaction.

Treatment of central neuropathic pain due to spinal cord injury

In the treatment of central neuropathic pain due to spinal cord injury the incidence of adverse reactions in general, central nervous system adverse reactions and especially somnolence was increased. This may be attributed to an additive effect due to concomitant medicinal products (e.g. anti-spasticity agents) needed for this condition. This should be considered when prescribing Zolyca in this condition.

Respiratory depression

There have been reports of severe respiratory depression in relation to Zolyca use. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of CNS depressants and the elderly may be at higher risk of experiencing this severe adverse reaction. Dose adjustments may be necessary in these patients. (see section 4.2)

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled studies of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for Zolyca.

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Reduced lower gastrointestinal tract function

There are post-marketing reports of events related to reduced lower gastrointestinal tract function (e.g., intestinal obstruction, paralytic ileus, constipation) when Zolyca was co-administered with medications that have the potential to produce constipation, such as opioid analgesics. When Zolyca and opioids will be used in combination, measures to prevent constipation may be considered (especially in female patients and elderly).

Concomitant use with opioids

Caution is advised when prescribing Zolyca concomitantly with opioids due to risk of CNS depression (see section 4.5). In a case-control study of opioid users, those patients who took Zolyca concomitantly with an opioid had an increased risk for opioid-related death compared to opioid use alone (adjusted odds ratio [aOR], 1.68 [95% CI, 1.19 – 2.36]). This increased risk was observed at low doses of Zolyca (≤ 300 mg, aOR 1.52 [95% CI, 1.04 – 2.22]) and there was a trend for a greater risk at high doses of Zolyca (> 300 mg, aOR 2.51 [95% CI 1.24 – 5.06]).

Misuse, abuse potential or dependence

Cases of misuse, abuse and dependence have been reported. Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of Zolyca misuse, abuse or dependence (development of tolerance, dose escalation, drug-seeking behaviour have been reported).

Encephalopathy

Cases of encephalopathy have been reported, mostly in patients with underlying conditions that may precipitate encephalopathy.

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported rarely in association with Zolyca treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, Zolyca should be withdrawn immediately and an alternative treatment considered (as appropriate).

Women of childbearing potential/Contraception

Zolyca use in the first-trimester of pregnancy may cause major birth defects in the unborn child. Zolyca should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus. Women of childbearing potential have to use effective contraception during treatment (see section 4.6).

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per each capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Since Zolyca is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), does not inhibit drug metabolism *in vitro*, and is not bound to plasma proteins, it is unlikely to produce, or be subject to, pharmacokinetic interactions.

In vivo studies and population pharmacokinetic analysis

Accordingly, in *in vivo* studies no clinically relevant pharmacokinetic interactions were observed between Zolyca and phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, lorazepam, oxycodone or ethanol. Population pharmacokinetic analysis indicated that oral antidiabetics, diuretics, insulin, phenobarbital, tiagabine and topiramate had no clinically significant effect on Zolyca clearance.

Oral contraceptives, norethisterone and/or ethinyl oestradiol

Co-administration of Zolyca with the oral contraceptives norethisterone and/or ethinyl oestradiol does not influence the steady-state pharmacokinetics of either substance.

Central nervous system influencing medical products

Zolyca may potentiate the effects of ethanol and lorazepam. In the postmarketing experience, there are reports of respiratory failure, coma and deaths in patients taking Zolyca and opioids and/or other central nervous system (CNS) depressant medicinal products. Zolyca appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.

Interactions and the elderly

No specific pharmacodynamic interaction studies were conducted in elderly volunteers. Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

Women of child bearing potential have to use effective contraception during treatment (see section 4.4).

Pregnancy

Studies in animals have shown reproductive toxicity (see section 5.3).

Zolyca has been shown to cross the placenta in rats (see section 5.2). Zolyca may cross the human placenta.

Major congenital malformations

Data from a Nordic observational study of more than 2700 pregnancies exposed to Zolyca in the first trimester showed a higher prevalence of major congenital malformations (MCM) among the paediatric population (live or stillborn) exposed to Zolyca compared to the unexposed population (5.9% vs. 4.1%).

The risk of MCM among the paediatric population exposed to Zolyca in the first trimester was slightly higher compared to unexposed population (adjusted prevalence ratio and 95% confidence interval: 1.14 (0.96-1.35)), and compared to population exposed to lamotrigine (1.29 (1.01–1.65)) or to duloxetine (1.39 (1.07–1.82)).

The analyses on specific malformations showed higher risks for malformations of the nervous system, the eye, orofacial clefts, urinary malformations and genital malformations, but numbers were small and estimates imprecise.

Zolycashould not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus).

Breast-feeding

Zolyca is excreted into human milk (see section 5.2). The effect of Zolyca on newborns/infants is unknown. A decision must be made whether to discontinue breast-feeding or to discontinue Zolyca therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no clinical data on the effects of Zolyca on female fertility.

In a clinical trial to assess the effect of Zolyca on sperm motility, healthy male subjects were exposed to Zolyca at a dose of 600 mg/day. After 3 months of treatment, there were no effects on sperm motility.

A fertility study in female rats has shown adverse reproductive effects. Fertility studies in male rats have shown adverse reproductive and developmental effects. The clinical relevance of these findings is unknown (see section 5.3).

4.7 Effects on ability to drive and use machines

Zolycamay have minor or moderate influence on the ability to drive and use machines. Zolycamay cause dizziness and somnolence and therefore may influence the ability to drive or use machines. Patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether this medicinal product affects their ability to perform these activities.

4.8 Undesirable effects

The Zolyca clinical programme involved over 8,900 patients exposed to Zolyca, of whom over 5,600 were in double-blind placebo controlled trials. The most commonly reported adverse reactions were dizziness and somnolence. Adverse reactions were usually mild to moderate in intensity. In all controlled studies, the discontinuation rate due to adverse reactions was 12% for patients receiving Zolyca and 5% for patients receiving placebo. The most common adverse reactions resulting in discontinuation from Zolyca treatment groups were dizziness and somnolence.

In table 2 below all adverse reactions, which occurred at an incidence greater than placebo and in more than one patient, are listed by class and frequency (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.

The adverse reactions listed may also be associated with the underlying disease and/or concomitant medicinal products.

In the treatment of central neuropathic pain due to spinal cord injury the incidence of adverse reactions in general, CNS adverse reactions and especially somnolence was increased (see section 4.4).

Additional reactions reported from post-marketing experience are included in italics in the list below.

Table 2. Zolyca adverse drug reactions

System Organ Class	Adverse drug reactions
Infections and infestations	
Common	Nasopharyngitis
Blood and lymphatic system disorders	
Uncommon	Neutropaenia
Immune system disorders	
Uncommon	*Hypersensitivity*
Rare	*Angioedema, allergic reaction*
Metabolism and nutrition disorders	
Common	Appetite increased
Uncommon	Anorexia, hypoglycaemia
Psychiatric disorders	
Common	Euphoric mood, confusion, irritability, libido decreased, disorientation, insomnia
Uncommon	Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, *aggression*, mood swings, depersonalisation, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy
Rare	Disinhibition,
Nervous system disorders	

Very Common	Dizziness, somnolence, headache
Common	Ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoaesthesia, sedation, balance disorder, lethargy
Uncommon	Syncope, stupor, myoclonus, *loss of consciousness*, psychomotor hyperactivity, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, *mental impairment*, speech disorder, hyporeflexia, hyperaesthesia, burning sensation*,* ageusia, *malaise*
Rare	*Convulsions*, hypokinesia, parosmia, dysgraphia, Parkinsonism
Eye disorders	
Common	Vision blurred, diplopia
Uncommon	Peripheral vision loss, Visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, lacrimation increased, eye irritation,
Rare	*Vision loss, keratitis,* oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness
Ear and labyrinth disorders	
Common	Vertigo
Uncommon	Hyperacusis
Cardiac disorders	
Uncommon	Tachycardia, atrioventricular block first degree, sinus bradycardia, *Congestive heart failure*
Rare	*QT prolongation*, sinus tachycardia, sinus arrhythmia
Vascular disorders	
Uncommon	Flushing, hot flushes, hypotension, hypertension, peripheral coldness
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness
Rare	*Pulmonary oedema*, throat tightness
Not known	Respiratory depression
Gastrointestinal disorders	
Common	*Vomiting, nausea*, dry mouth, constipation, *diarrhoea,* flatulence, abdominal distension
Uncommon	Gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral
Rare	Ascites, pancreatitis, dysphagia, *Swollen tongue*
Hepatobiliary disorders	
Uncommon	Elevated liver enzymes*
Rare	Jaundice
Very rare	Hepatic failure, hepatitis
Skin and subcutaneous tissue disorders	
Uncommon	Rash papular, hyperhidrosis, urticaria, pruritus
Rare	*Stevens Johnson syndrome*, cold sweat, Toxic Epidermal Necrolysis
Musculoskeletal and connective tissue disorders	
Common	Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm
Uncommon	Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness

Rare	Rhabdomyolysis
Renal and urinary disorders	
Uncommon	Urinary incontinence, dysuria
Rare	Renal failure, oliguria, *urinary retention*
Reproductive system and breast disorders	
Common	Erectile dysfunction
Uncommon	Ejaculation delayed, sexual dysfunction, dysmenorrhoea, breast pain
Rare	Amenorrhoea, breast discharge, breast enlargement, *gynaecomastia*
General disorders and administration site conditions	
Common	Gait abnormal, feeling drunk, fatigue, oedema peripheral, oedema, fall, feeling abnormal
Uncommon	Generalised oedema, pyrexia, *face oedema*, chest tightness, pain, thirst, chills, asthenia
Investigations	
Common	Weight increased
Uncommon	Blood creatine phosphokinase increased, blood glucose increased, platelet count decreased, blood creatinine increased, blood potassium decreased, weight decreased.
Rare	White blood cell count decreased

* Alanine aminotransferase increased (ALT) and aspartate aminotransferase increased (AST).

After discontinuation of short-term and long-term treatment with Zolyca withdrawal symptoms have been observed in some patients. The following reactions have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, convulsions, nervousness, depression, pain, hyperhidrosis and dizziness suggestive of physical dependence. The patient should be informed about this at the start of the treatment.

Concerning discontinuation of long-term treatment of Zolyca, data suggest that the incidence and severity of withdrawal symptoms may be dose-related.

Paediatric population

The Zolyca safety profile observed in five paediatric studies in patients with partial seizures with or without secondary generalisation (12-week efficacy and safety study in patients 4 to 16 years of age, n=295; 14-day efficacy and safety study in patients 1 month to younger than 4 years of age, n=175;pharmacokinetic and tolerability study, n=65; and two 1 year open label follow on safety studies, n=54 and n=431) was similar to that observed in the adult studies of patients with epilepsy. The most common adverse events observed in the 12-week study with Zolyca treatment were somnolence, pyrexia, upper respiratory tract infection, increased appetite, weight increased, and nasopharyngitis. The most common adverse events observed in the 14-day study with Zolyca treatment were somnolence, upper respiratory tract infection, and pyrexia (see sections 4.2, 5.1 and 5.2).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In the post-marketing experience, the most commonly reported adverse reactions observed when Zolyca was taken in overdose included somnolence, confusional state, agitation, and restlessness. Seizures were also reported.

In rare occasions, cases of coma have been reported.

Treatment of Zolyca overdose should include general supportive measures and may include haemodialysis if necessary (see section 4.2 Table 1).

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, other antiepileptics ATC code: N03AX16

The active substance, Zolyca, is a gamma-aminobutyric acid analogue ((S)-3-(aminomethyl)-5- methylhexanoic acid).

Mechanism of action

Zolyca binds to an auxiliary subunit (α_2-δ protein) of voltage-gated calcium channels in the central nervous system.

Clinical Efficacy and safety

Neuropathic pain

Efficacy has been shown in trials in diabetic neuropathy, post herpetic neuralgia and spinal cord injury. Efficacy has not been studied in other models of neuropathic pain.

Zolyca has been studied in 10 controlled clinical trials of up to 13 weeks with twice a day dosing (BID) and up to 8 weeks with three times a day (TID) dosing. Overall, the safety and efficacy profiles for BID and TID dosing regimens were similar.

In clinical trials up to 12 weeks for both peripheral and central neuropathic pain, a reduction in pain was seen by week 1 and was maintained throughout the treatment period.

In controlled clinical trials in peripheral neuropathic pain 35% of the Zolyca treated patients and 18% of the patients on placebo had a 50% improvement in pain score. For patient's not experiencing somnolence, such an improvement was observed in 33% of patients treated with Zolyca and 18% of patients on placebo. For patients who experienced somnolence the responder rates were 48% on Zolyca and 16% on placebo.

In the controlled clinical trial in central neuropathic pain 22% of the Zolyca treated patients and 7% of the patients on placebo had a 50% improvement in pain score.

Epilepsy

Adjunctive Treatment

Zolyca has been studied in 3 controlled clinical trials of 12 week duration with either twice a day dosing (BID) or three times a day (TID) dosing. Overall, the safety and efficacy profiles for BID and TID dosing regimens were similar.

A reduction in seizure frequency was observed by Week 1.

Paediatric population

The efficacy and safety of Zolyca as adjunctive treatment for epilepsy in paediatric patients below the age of 12 and adolescents has not been established. The adverse events observed in a pharmacokinetic and tolerability study that enrolled patients from 3 months to 16 years of age (n=65) with partial onset seizures were similar to those observed in adults. Results of a 12-week placebo-controlled study of 295 paediatric patients aged 4 to 16 years and a 14-day placebo-controlled study of 175 paediatric patients aged 1 month to younger than 4 years of age performed to evaluate the efficacy and safety of Zolyca as adjunctive therapy for the treatment of partial onset seizures and two 1 year open label safety studies in 54 and 431 paediatric patients respectively, from 3 months to 16 years of age with epilepsy indicate that the adverse events of pyrexia and upper respiratory infections were observed more frequently than in adult studies of patients with epilepsy (see sections 4.2, 4.8 and 5.2).

In the 12-week placebo-controlled study, paediatric patients (4 to 16 years of age) were assigned to Zolyca 2.5 mg/kg/day (maximum, 150 mg/day), Zolyca 10 mg/kg/day (maximum, 600 mg/day), or placebo. The percentage of subjects with at least a 50% reduction in partial onset seizures as compared to baseline was

40.6% of subjects treated with Zolyca 10 mg/kg/day (p=0.0068 versus placebo), 29.1% of subjects treated with Zolyca 2.5 mg/kg/day (p=0.2600 versus placebo) and 22.6% of those receiving placebo.

In the 14-day placebo-controlled study, paediatric patients (1 month to younger than 4 years of age) were assigned to Zolyca 7 mg/kg/day, Zolyca 14 mg/kg/day, or placebo. Median 24-hour seizure frequencies at baseline and at the final visit were 4.7 and 3.8 for Zolyca 7 mg/kg/day, 5.4 and 1.4 for Zolyca 14 mg/kg/day, and 2.9 and 2.3 for placebo, respectively. Zolyca 14 mg/kg/day significantly reduced the log-transformed partial onset seizure frequency versus placebo (p=0.0223); Zolyca 7 mg/kg/day did not show improvement relative to placebo.

In a 12-week placebo-controlled study in subjects with Primary Generalized Tonic-Clonic (PGTC) seizures 219 subjects (aged 5 to 65 years, of which 66 were aged 5 to 16 years) were assigned to Zolyca 5 mg/kg/day (maximum 300 mg/day), 10 mg/kg/day (maximum 600 mg/day) or placebo as adjunctive therapy. The percentage of subjects with at least a 50% reduction in PGTC seizure rate was 41.3%, 38.9% and 41.7% for Zolyca 5 mg/kg/day, Zolyca 10 mg/kg/day and placebo respectively.

Monotherapy (newly diagnosed patients)

Zolyca has been studied in 1 controlled clinical trial of 56 week duration with twice a day dosing (BID). Zolyca did not achieve non-inferiority to lamotrigine based on the 6-month seizure freedom endpoint. Zolyca and lamotrigine were similarly safe and well tolerated.

Generalised Anxiety Disorder

Zolyca has been studied in 6 controlled trials of 4-6 week duration, an elderly study of 8 week duration and a long-term relapse prevention study with a double blind relapse prevention phase of 6 months duration.

Relief of the symptoms of GAD as reflected by the Hamilton Anxiety Rating Scale (HAM-A) was observed by Week 1.

In controlled clinical trials (4-8 week duration) 52% of the Zolyca treated patients and 38% of the patients on placebo had at least a 50% improvement in HAM-A total score from baseline to endpoint.

In controlled trials, a higher proportion of patients treated with Zolyca reported blurred vision than did patients treated with placebo which resolved in a majority of cases with continued dosing. Ophthalmologic testing (including visual acuity testing, formal visual field testing and dilated funduscopic examination) was conducted in over 3600 patients within controlled clinical trials. In these patients, visual acuity was reduced in 6.5% of patients treated with Zolyca, and 4.8% of placebo-treated patients. Visual field changes were detected in 12.4% of Zolyca-treated, and 11.7% of placebo-treated patients. Funduscopic changes were observed in 1.7% of Zolyca-treated and 2.1% of placebo-treated patients.

5.2 Pharmacokinetic properties

Zolyca steady-state pharmacokinetics are similar in healthy volunteers, patients with epilepsy receiving anti-epileptic drugs and patients with chronic pain.

Absorption

Zolyca is rapidly absorbed when administered in the fasted state, with peak plasma concentrations occurring within 1 hour following both single and multiple dose administration. Zolyca oral bioavailability is estimated to be ≥ 90% and is independent of dose. Following repeated administration, steady state is achieved within 24 to 48 hours. The rate of Zolyca absorption is decreased when given with food resulting in a decrease in C_{max} by approximately 25-30% and a delay in t_{max} to approximately 2.5 hours. However, administration of Zolyca with food has no clinically significant effect on the extent of Zolyca absorption.

Distribution

In preclinical studies, Zolyca has been shown to cross the blood brain barrier in mice, rats, and monkeys. Zolyca has been shown to cross the placenta in rats and is present in the milk of lactating rats. In humans, the apparent volume of distribution of Zolyca following oral administration is approximately 0.56 l/kg. Zolyca is not bound to plasma proteins.

Biotransformation

Zolyca undergoes negligible metabolism in humans. Following a dose of radiolabelled Zolyca, approximately 98% of the radioactivity recovered in the urine was unchanged Zolyca. The N- methylated derivative of Zolyca, the major metabolite of Zolyca found in urine, accounted for 0.9% of the dose. In preclinical studies, there was no indication of racemisation of Zolyca S- enantiomer to the R-enantiomer.

Elimination

Zolyca is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. Zolyca mean elimination half-life is 6.3 hours. Zolyca plasma clearance and renal clearance are directly proportional to creatinine clearance (see section 5.2 Renal impairment).

Dose adjustment in patients with reduced renal function or undergoing haemodialysis is necessary (see section 4.2 Table 1).

Linearity/ non-linearity

Zolyca pharmacokinetics are linear over the recommended daily dose range. Inter-subject pharmacokinetic variability for Zolyca is low (<20%). Multiple dose pharmacokinetics are predictable from single-dose data. Therefore, there is no need for routine monitoring of plasma concentrations of Zolyca.

Gender

Clinical trials indicate that gender does not have a clinically significant influence on the plasma concentrations of Zolyca.

Renal impairment

Zolyca clearance is directly proportional to creatinine clearance. In addition, Zolyca is effectively removed from plasma by haemodialysis (following a 4 hour haemodialysis treatment plasma Zolyca concentrations are reduced by approximately 50%). Because renal elimination is the major elimination pathway, dose reduction in patients with renal impairment and dose supplementation following haemodialysis is necessary (see section 4.2 Table 1).

Hepatic impairment

No specific pharmacokinetic studies were carried out in patients with impaired liver function. Since Zolyca does not undergo significant metabolism and is excreted predominantly as unchanged drug in the urine, impaired liver function would not be expected to significantly alter Zolyca plasma concentrations.

Paediatric population

Zolyca pharmacokinetics were evaluated in paediatric patients with epilepsy (age groups: 1 to 23 months, 2 to 6 years, 7 to 11 years and 12 to 16 years) at dose levels of 2.5, 5, 10 and 15 mg/kg/day in a pharmacokinetic and tolerability study.

After oral administration of Zolyca in paediatric patients in the fasted state, in general, time to reach peak plasma concentration was similar across the entire age group and occurred 0.5 hours to 2 hours postdose.

Zolyca Cmax and AUC parameters increased in a linear manner with increasing dose within each age group. The AUC was lower by 30% in paediatric patients below a weight of 30 kg due to an increased body weight adjusted clearance of 43% for these patients in comparison to patients weighing ≥30 kg.

Zolyca terminal half-life averaged about 3 to 4 hours in paediatric patients up to 6 years of age, and 4 to 6 hours in those 7 years of age and older.

Population pharmacokinetic analysis showed that creatinine clearance was a significant covariate of Zolyca oral clearance, body weight was a significant covariate of Zolyca apparent oral volume of distribution, and these relationships were similar in paediatric and adult patients.

Zolyca pharmacokinetics in patients younger than 3 months old have not been studied (see sections 4.2, 4.8 and 5.1).

Elderly

Zolyca clearance tends to decrease with increasing age. This decrease in Zolyca oral clearance is consistent with decreases in creatinine clearance associated with increasing age. Reduction of Zolyca dose may be required in patients who have age related compromised renal function (see section 4.2 Table 1).

Breast-feeding mothers

The pharmacokinetics of 150 mg Zolyca given every 12 hours (300 mg daily dose) was evaluated in 10 lactating women who were at least 12 weeks postpartum. Lactation had little to no influence on Zolyca pharmacokinetics. Zolyca was excreted into breast milk with average steady-state concentrations approximately 76% of those in maternal plasma. The estimated infant dose from breast milk (assuming mean milk consumption of 150 mL/kg/day) of women receiving 300 mg/day or the maximum dose of 600 mg/day would be 0.31 or 0.62 mg/kg/day, respectively. These estimated doses are approximately 7% of the total daily maternal dose on a mg/kg basis.

5.3 Preclinical safety data

In conventional safety pharmacology studies in animals, Zolyca was well-tolerated at clinically relevant doses. In repeated dose toxicity studies in rats and monkeys CNS effects were observed, including hypoactivity, hyperactivity and ataxia. An increased incidence of retinal atrophy commonly observed in aged albino rats was seen after long term exposure to Zolyca at exposures ≥ 5 times the mean human exposure at the maximum recommended clinical dose.

Zolyca was not teratogenic in mice, rats or rabbits. Foetal toxicity in rats and rabbits occurred only at exposures sufficiently above human exposure. In prenatal/postnatal toxicity studies, Zolyca induced offspring developmental toxicity in rats at exposures >2 times the maximum recommended human exposure.

Adverse effects on fertility in male and female rats were only observed at exposures sufficiently in excess of therapeutic exposure. Adverse effects on male reproductive organs and sperm parameters were reversible and occurred only at exposures sufficiently in excess of therapeutic exposure or were associated with spontaneous degenerative processes in male reproductive organs in the rat. Therefore the effects were considered of little or no clinical relevance.

Zolyca is not genotoxic based on results of a battery of *in vitro* and *in vivo* tests.

Two-year carcinogenicity studies with Zolyca were conducted in rats and mice. No tumours were observed in rats at exposures up to 24 times the mean human exposure at the maximum recommended clinical dose of 600 mg/day. In mice, no increased incidence of tumours was found at exposures similar to the mean human exposure, but an increased incidence of haemangiosarcoma was observed at higher exposures. The non-genotoxic mechanism of Zolyca-induced tumour formation in mice involves platelet changes and associated endothelial cell proliferation. These platelet changes were not present in rats or in humans based on short term and limited long term clinical data. There is no evidence to suggest an associated risk to humans.

In juvenile rats the types of toxicity do not differ qualitatively from those observed in adult rats. However, juvenile rats are more sensitive. At therapeutic exposures, there was evidence of CNS clinical signs of hyperactivity and bruxism and some changes in growth (transient body weight gain suppression). Effects on the oestrus cycle were observed at 5-fold the human therapeutic exposure. Reduced acoustic startle response was observed in juvenile rats 1-2 weeks after exposure at >2 times the human therapeutic exposure. Nine weeks after exposure, this effect was no longer observable.

6. Pharmaceutical particulars

6.1 List of excipients

Capsules content:

Maize starch

Talc

Capsules shell:

Titanium Dioxide (E171)

Gelatin

Sodium Lauryl sulfate

Iron oxide Red (E 172)

Printing Ink:

Shellac

Propylene Glycol

Black Iron Oxide (E172)

Potassium Hydroxide

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 storage conditions.

6.5 Nature and contents of container
Zolycahard capsules are available in clear PVC/ Aluminium blisters pack and white opaque HDPE bottles with polypropylene closure.

Pack sizes:

Blister packs: 14, 21, 30, 56, 60, 84, 90, 100, 112 and 200 capsules, hard

HDPE Bottle packs: 30, 200, 250 and 500 capsules, hard

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

ZOLON HEALTHCARE LIMITED, NO 9/11 EDIC BULIDING TOWN PLANNING WAY, ILUPEJU

8. Manufacturer
Zolon
Healthcare
Limited, Lagos.