# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Zonisamide Milpharm 100 mg Hard Capsules

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 100 mg of zonisamide.

Excipient(s) with known effect

Each hard capsule contains 0.0009 mg of FD & C Yellow 6 (E110) and 0.1426 mg of FD & C Red 40 (E129).

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Hard capsule.

Red opaque cap and white to off-white opaque body, size ‘1’ hard gelatin capsules imprinted with ‘ZN’ on cap and ‘100’ on body, filled with white to off-white powder.

Size: about 19.3 mm

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Zonisamide is indicated as:

- monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy (see section 5.1);

- adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation, in adults, adolescents, and children aged 6 years and above.

## 4.2 Posology and method of administration

Posology - Adults

*Dosage escalation and maintenance*

Zonisamide may be taken as monotherapy or added to existing therapy in adults. The dose should be titrated on the basis of clinical effect. Recommended escalation and maintenance doses are given in Table 1. Some patients, especially those not taking CYP3A4-inducing agents, may respond to lower doses.

*Withdrawal*

When Zonisamide treatment is to be discontinued, it should be withdrawn gradually (see section 4.4). In clinical studies of adult patients, dose reductions of 100 mg at weekly intervals have been used with concurrent adjustment of other antiepileptic medicine doses (where necessary).

**Table 1. Adults – recommended dosage escalation and maintenance regimen**

| **Treatment Regimen** | **Titration Phase** | | | **Usual Maintenance Dose** |
|---|---|---|---|---|
| **Monotherapy** - Newly diagnosed adult patients | **Week 1 + 2** | **Week 3 + 4** | **Week 5 + 6** | 300 mg per day (once a day).<br>If a higher dose is required: increase at two-weekly intervals in increments of 100 mg up to a maximum of 500 mg. |
| | 100 mg/day (once a day) | 200 mg /day (once a day) | 300 mg / day (once a day) | |
| **Adjunctive therapy**<br>- with CYP3A4-inducing agents (see section 4.5) | **Week 1** | **Week 2** | **Week 3 to 5** | 300 to 500 mg per day<br>(once a day or two divided doses). |
| | 50 mg/day (in two divided doses) | 100 mg /day (in two divided doses) | Increase at weekly intervals in increments of 100 mg | |
| - without CYP3A4- | **Week 1 + 2** | **Week 3 + 4** | **Week 5 to 10** | 300 to 500 mg per |

| | | | | |
|---|---|---|---|---|
| inducing agents; or with renal or hepatic impairment | 50 mg/day (in two divided doses) | 100 mg / day (in two divided doses) | Increase at two-weekly intervals in increments of up to 100 mg | day (once a day or two divided doses). Some patients may respond to lower doses. |

General dosing recommendations for Zonisamide in special patient populations

*Paediatric population (aged 6 years and above)*

*Dosage escalation and maintenance*

Zonisamide must be added to existing therapy for paediatric patients aged 6 years and above. The dose should be titrated on the basis of clinical effect. Recommended escalation and maintenance doses are given in Table 2. Some patients, especially those not taking CYP3A4-inducing agents, may respond to lower doses.

Physicians should draw the attention of paediatric patients and their parents/carers to the Patient Alert Box (in the package leaflet) on preventing heatstroke (see section 4.4: Paediatric population).

**Table 2. Paediatric population (aged 6 years and above) – recommended dosage escalation and maintenance regimen**

<table>
<tr><th>Treatment Regimen</th><th colspan="2">Titration Phase</th><th colspan="2">Usual Maintenance Dose</th></tr>
<tr><td rowspan="2">Adjunctive therapy<br>- with CYP3A4-inducing agents (see section 4.5)</td><td>Week 1</td><td>Weeks 2 to 8</td><td>Patients of weight 20 to 55 kg[a]</td><td>Patients of weight > 55 kg</td></tr>
<tr><td>1 mg/kg/day (once a day)</td><td>Increase at weekly intervals in increments of 1 mg/kg</td><td>6 to 8 mg/kg/day (once a day)</td><td>300 - 500 mg/day (once a day)</td></tr>
<tr><td rowspan="2">- without CYP3A4-inducing agents</td><td>Week 1 + 2</td><td>Weeks ≥ 3</td><td rowspan="2">6 to 8 mg/kg/day (once a day)</td><td rowspan="2">300 - 500 mg/day (once a day)</td></tr>
<tr><td>1 mg/kg/day (once a day)</td><td>Increase at two-weekly intervals in increments of 1 mg/kg</td></tr>
</table>

**Note:**

a. To ensure a therapeutic dose is maintained the weight of a child should be monitored and the dose reviewed as weight changes occur up to a weight of 55kg. The dose regime is 6-8 mg/kg/day up to a maximum dose of 500 mg/day.

The safety and efficacy of Zonisamide in children aged below 6 years or those below 20 kg have not yet been established.

There are limited data from clinical studies in patients with a body weight of less than 20 kg. Therefore children aged 6 years and above and with a body weight less than 20 kg should be treated with caution.

It is not always possible to precisely achieve the calculated dose with the commercially available capsule strengths of Zonisamide. In these cases it is therefore recommended that the Zonisamide total dose should be rounded up or down to the

nearest available dose that can be achieved with commercially available capsule strengths of Zonisamide (25 mg, 50 mg and 100 mg).

*Withdrawal*

When Zonisamide treatment is to be discontinued, it should be withdrawn gradually (see section 4.4). In clinical studies of paediatric patients, down-titration was completed by dose reductions at weekly intervals in increments of about 2 mg/kg (i.e. in accordance with the schedule in Table 3).

**Table 3. Paediatric population (aged 6 years and above) – recommended down-titration schedule**

| **Weight** | **Decrease at weekly intervals in increments of:** |
|---|---|
| 20 – 28 kg | 25 to 50 mg / day* |
| 29 – 41 kg | 50 to 75 mg / day* |
| 42 – 55 kg | 100 mg / day* |
| >55 kg | 100 mg / day* |

Note:

* All doses are once daily.

*Elderly*

Caution should be exercised at initiation of treatment in elderly patients as there is limited information on the use of Zonisamide in these patients. Prescribers should also take account of the safety profile of Zonisamide (see section 4.8).

*Patients with renal impairment*

Caution must be exercised in treating patients with renal impairment, as there is limited information on use in such patients and a slower titration of Zonisamide might be required. Since zonisamide and its metabolites are excreted renally, it should be discontinued in patients who develop acute renal failure or where a clinically significant sustained increase in serum creatinine is observed.

In subjects with renal impairment, renal clearance of single doses of zonisamide was positively correlated with creatinine clearance. The plasma AUC of zonisamide was increased by 35% in subjects with creatinine clearance < 20 ml/min.

*Patients with hepatic impairment*

Use in patients with hepatic impairment has not been studied. Therefore use in patients with severe hepatic impairment is not recommended. Caution must be exercised in treating patients with mild to moderate hepatic impairment, and a slower titration of Zonisamide may be required.

Method of administration

Zonisamide hard capsules are for oral use.

*Effect of food*

Zonisamide may be taken with or without food (see section 5.2).

## 4.3 Contraindications

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

## 4.4 Special warnings and precautions for use

Unexplained rash

**Serious rashes occur in association with Zonisamide therapy, including cases of Stevens-Johnson syndrome.**

Consideration must be given to discontinuing Zonisamide in patients who develop an otherwise unexplained rash. All patients who develop a rash while taking Zonisamide must be closely supervised, with additional levels of caution applied to those patients receiving concomitant antiepileptic agents that may independently induce skin rashes.

Withdrawal seizures

In accordance with current clinical practice, discontinuation of Zonisamide in patients with epilepsy must be accomplished by gradual dose reduction, to reduce the possibility of seizures on withdrawal. There are insufficient data for the withdrawal of concomitant antiepileptic medicines once seizure control with Zonisamide has been achieved in the add-on situation, in order to reach monotherapy with Zonisamide. Therefore, withdrawal of concomitant anti-epileptic medicinal products must be undertaken with caution.

Sulphonamide reactions

Zonisamide is a benzisoxazole derivative, which contains a sulphonamide group. Serious immune based adverse reactions that are associated with medicinal products containing a sulphonamide group include rash, allergic reaction and major haematological disturbances, including aplastic anaemia, which very rarely can be fatal.

Cases of agranulocytosis, thrombocytopenia, leukopenia, aplastic anaemia, pancytopenia and leucocytosis have been reported. There is inadequate information to assess the relationship, if any, between dose and duration of treatment and these events.

Acute myopia and secondary angle closure glaucoma

A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in adult and paediatric patients receiving zonisamide. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, and ocular hyperaemia (redness) and increased intraocular pressure. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle

closure glaucoma. Symptoms may occur within hours to weeks of initiating therapy. Treatment includes discontinuation of zonisamide, as rapidly as possible in the judgment of the treating physician, and appropriate measures to reduce intraocular pressure. Elevated intraocular pressure of any aetiology, if left untreated, can lead to serious sequelae including permanent vision loss. Caution should be used when treating patients with history of eye disorders with zonisamide.

Suicide 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 trials of anti-epileptic medicinal products 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 Zonisamide.

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.

Kidney stones

Some patients, especially those with a predisposition to nephrolithiasis, may be at increased risk for renal stone formation and associated signs and symptoms such as renal colic, renal pain or flank pain. Nephrolithiasis may lead to chronic kidney damage. Risk factors for nephrolithiasis include prior stone formation, a family history of nephrolithiasis and hypercalciuria. None of these risk factors can reliably predict stone formation during zonisamide treatment. In addition, patients taking other medications associated with nephrolithiasis may be at increased risk. Increasing fluid intake and urine output may help reduce the risk of stone formation, particularly in those with predisposing risk factors.

Metabolic acidosis

Hyperchloraemic, non-anion gap, metabolic acidosis (i.e. decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis) is associated with Zonisamide treatment. This metabolic acidosis is caused by renal bicarbonate loss due to the inhibitory effect of zonisamide on carbonic anhydrase. Such electrolyte imbalance has been observed with the use of Zonisamide in placebo-controlled clinical trials and in the post-marketing period. Generally, zonisamide-induced metabolic acidosis occurs early in treatment although cases can occur at any time during treatment. The amounts by which bicarbonate is decreased are usually small – moderate (average decrease of approximately 3.5 mEq/l at daily doses of 300 mg in adults); rarely patients can experience more severe decreases. Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhoea, surgery, ketogenic diet, or medicinal products) may be additive to the bicarbonate lowering effects of zonisamide.

The risk of zonisamide induced metabolic acidosis appears to be more frequent and severe in younger patients. Appropriate evaluation and monitoring of serum bicarbonate levels should be carried out in patients taking zonisamide who have underlying conditions which might increase the risk of acidosis, in patients who are at an increased risk of adverse consequences of metabolic acidosis and in patients with symptoms suggestive of metabolic acidosis. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing Zonisamide (by gradual discontinuation or reduction of a therapeutic dose) as osteopenia may develop.

If the decision is made to continue patients on Zonisamide in the face of persistent acidosis, alkali treatment should be considered.

Metabolic acidosis has the potential to lead to hyperammonaemia, which has been reported with or without encephalopathy during zonisamide treatment. The risk for hyperammonaemia may be increased in patients concomitantly taking other medications that can cause hyperammonaemia (e.g. valproate), or who have an underlying urea cycle disorder or reduced hepatic mitochondrial activity. In patients who develop unexplained lethargy or changes in mental status during treatment with zonisamide, it is recommended to consider hyperammonaemic encephalopathy and to measure ammonia levels.

Zonisamide should be used with caution in adult patients being treated concomitantly with carbonic anhydrase inhibitors such as topiramate or acetazolamide, as there are insufficient data to rule out a pharmacodynamic interaction (see also section 4.4 Paediatric population and section 4.5).

Heat stroke

Cases of decreased sweating and elevated body temperature have been reported mainly in paediatric patients (see section 4.4 Paediatric population for full warning). Caution should be used in adults when Zonisamide is prescribed with other medicinal products that predispose patients to heat related disorders; these include carbonic anhydrase inhibitors and medicinal products with anticholinergic activity (see also section 4.4 Paediatric population).

Pancreatitis

In patients taking Zonisamide who develop the clinical signs and symptoms of pancreatitis, it is recommended that pancreatic lipase and amylase levels are monitored. If pancreatitis is evident, in the absence of another obvious cause, it is recommended that discontinuation of Zonisamide be considered and appropriate treatment initiated.

Rhabdomyolysis

In patients taking Zonisamide, in whom severe muscle pain and/or weakness develop either in the presence or absence of a fever, it is recommended that markers of muscle damage be assessed, including serum creatine phosphokinase and aldolase levels. If elevated, in the absence of another obvious cause such as trauma or grand mal seizures, it is recommended that

Zonisamide discontinuation be considered and appropriate treatment initiated.

Women of childbearing potential

Women of childbearing potential must use effective contraception during treatment with Zonisamide and for one month after discontinuation (see section 4.6). Zonisamide must not be used in women of childbearing potential not using effective contraception unless clearly necessary and only if the potential benefit is considered to justify the risk to the foetus. Specialist medical advice should be given to women treated with Zonisamide who are of childbearing potential. The woman should be fully informed of and understand the possible effects of Zonisamide on the foetus and these risks should be discussed with the patient in relation to the benefits before starting treatment. Before the initiation of treatment with Zonisamide in a woman of childbearing potential, pregnancy testing should be considered. Women planning a pregnancy should meet with their specialists to reassess treatment with Zonisamide and to consider other therapeutic options prior to conception and before contraception is discontinued. Women of childbearing potential should be counselled to contact her doctor immediately if she becomes pregnant or thinks she may be pregnant and is taking Zonisamide. Physicians treating patients with Zonisamide should ensure that patients are fully informed about the need to use appropriate effective contraception and should use clinical judgement when assessing whether oral contraceptives (OCs), or the doses of the OC components, are adequate based on the individual patient's clinical situation.

Body weight

Zonisamide may cause weight loss. A dietary supplement or increased food intake may be considered if the patient is losing weight or is underweight whilst on this medication. If substantial undesirable weight loss occurs, discontinuation of Zonisamide should be considered. Weight loss is potentially more serious in children (see section 4.4. Paediatric population).

Paediatric population

The warnings and precautions mentioned above are also applicable to adolescent and paediatric patients. The warnings and precautions mentioned below are more relevant to paediatric and adolescent patients.

*Heat stroke and dehydration*

Preventing overheating and dehydration in children
Zonisamide can cause children to sweat less and overheat and if the child is not treated this can lead to brain damage and death. Children are most at risk especially in hot weather.
When a child is taking Zonisamide:
• The child should stay cool especially in hot weather
• The child must avoid heavy exercise especially when the weather is hot
• The child must drink plenty of cold water
• The child must not take any of these medicines:
carbonic anhydrase inhibitors (like topiramate and acetazolamide), and anticholinergic agents (like clomipramine, hydroxyzine, diphenhydramine, haloperidol, imipramine and oxybutynin).
**IF ANY OF THE FOLLOWING OCCUR, THE CHILD NEEDS URGENT MEDICAL ATTENTION:**
The skin feels very hot with little or no sweating, or the child becomes confused or has muscle cramps, or the child's heartbeat or breathing become rapid.
• Take the child to a cool, shaded place
• Keep the child's skin cool with water
• Give the child cold water to drink

Cases of decreased sweating and elevated body temperature have been reported mainly in paediatric patients. Heat stroke requiring hospital treatment was diagnosed in some cases. Heat stroke requiring hospital treatment and leading to death has been reported. Most reports occurred during periods of warm weather. Physicians should discuss with patients and their carers the potential seriousness of heat stroke, situations in which it might arise, as well as action to take in the event of any signs or symptoms. Patients or their carers must be warned to take care to maintain hydration and avoid exposure to excessive temperatures and strenuous physical exercise depending on the condition of the patient. Prescribers should draw the attention of paediatric patients and their parent/ carers to the advice in the Packaging Leaflet on preventing heat stroke and overheating in children as provided. In the event of signs or symptoms of dehydration, oligohydrosis, or elevated body temperature, discontinuation of Zonisamide should be considered.

Zonisamide should not be used as co-medication in paediatric patients with other medicinal products that predispose patients to heat related disorders; these include carbonic anhydrase inhibitors and medicinal products with anticholinergic activity.

*Body weight*

Weight loss leading to deterioration of general condition and failure to take anti-epilepsy medication has been related to a fatal outcome (see section 4.8). Zonisamide is not recommended for paediatric patients who are underweight (definition in accordance with the WHO age adjusted BMI categories) or have a decreased appetite.

The incidence of decreased body weight is consistent across age groups (see section 4.8); however, given the potential seriousness of weight loss in

children, weight should be monitored in this population. A dietary supplement or increased food intake should be considered if the patient is failing to gain weight in accordance with growth charts, otherwise Zonisamide should be discontinued.

There are limited data from clinical studies in patients with a body weight of less than 20 kg. Therefore children aged 6 years and above with a body weight of less than 20 kg should be treated with caution. The long term effect of weight loss in the paediatric population on growth and development is unknown.

*Metabolic acidosis*

The risk of zonisamide induced metabolic acidosis appears to be more frequent and severe in paediatric and adolescent patients. Appropriate evaluation and monitoring of serum bicarbonate levels should be carried out in this population (see section 4.4 - Metabolic acidosis for full warning; see section 4.8 for incidence of low bicarbonate). The long term effect of low bicarbonate levels on growth and development is unknown.

Zonisamide should not be used as co-medication in paediatric patients with other carbonic anhydrase inhibitors such as topiramate and acetazolamide (see section 4.5).

*Kidney stones*

Kidney stones have occurred in paediatric patients (see section 4.4 Kidney stones for full warning).

Some patients, especially those with a predisposition to nephrolithiasis, may be at increased risk for renal stone formation and associated signs and symptoms such as renal colic, renal pain or flank pain. Nephrolithiasis may lead to chronic kidney damage. Risk factors for nephrolithiasis include prior stone formation, a family history of nephrolithiasis and hypercalciuria. None of these risk factors can reliably predict stone formation during zonisamide treatment.

Increasing fluid intake and urine output may help reduce the risk of stone formation, particularly in those with predisposing risk factors. Renal ultrasound should be performed at the discretion of the physician. In the event kidney stones are detected, Zonisamide should be discontinued.

*Hepatic dysfunction*

Increased levels of hepatobiliary parameters such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT) and bilirubin have occurred in paediatric and adolescent patients, without any consistent pattern in the observations of values above the upper limit of normal. Nevertheless, if a hepatic event is suspected, liver function should be evaluated and discontinuation of Zonisamide should be considered.

*Cognition*

Cognitive impairment in patients affected by epilepsy has been associated with the underlying pathology and/ or the administration of anti-epileptic treatment. In a zonisamide placebo-controlled study conducted in paediatric

and adolescent patients, the proportion of patients with impaired cognition was numerically greater in the zonisamide group compared with the placebo group.

**Zonisamide Milpharm 100 mg hard capsules contain Azo colouring agents**

Zonisamide Milpharm 100 mg hard capsules contain FD & C Yellow 6 (E110) and FD & C Red 40 (E129) which may cause allergic reactions.

## 4.5 Interaction with other medicinal products and other forms of interaction

*Effect of Zonisamide on cytochrome P450 enzymes*

*In vitro* studies using human liver microsomes show no or little (<25%) inhibition of cytochrome P450 isozymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A4 at zonisamide levels approximately two-fold or greater than clinically relevant unbound serum concentrations. Therefore, Zonisamide is not expected to affect the pharmacokinetics of other medicinal products via cytochrome P450-mediated mechanisms, as demonstrated for carbamazepine, phenytoin, ethinylestradiol and desipramine *in vivo*.

*Potential for Zonisamide to affect other medicinal products*

*Anti-epileptic medicinal products*

In epileptic patients, steady-state dosing with Zonisamide resulted in no clinically relevant pharmacokinetic effects on carbamazepine, lamotrigine, phenytoin, or sodium valproate.

*Oral contraceptives*

In clinical studies in healthy subjects, steady-state dosing with Zonisamide did not affect serum concentrations of ethinylestradiol or norethisterone in a combined oral contraceptive.

*Carbonic anhydrase inhibitors*

Zonisamide should be used with caution in adult patients treated concomitantly with carbonic anhydrase inhibitors such as topiramate and acetazolamide, as there are insufficient data to rule out a possible pharmacodynamic interaction (see section 4.4).

Zonisamide should not be used as co-medication in paediatric patients with other carbonic anhydrase inhibitors such as topiramate and acetazolamide (see section 4.4 Paediatric population).

*P-gp substrate*

An *in vitro* study shows that zonisamide is a weak inhibitor of P-gp (MDR1) with an $IC_{50}$ of 267 µmol/l and there is the theoretical potential for zonisamide to affect the pharmacokinetics of substances which are P-gp substrates. Caution is advised when starting or stopping zonisamide treatment or changing the zonisamide dose in patients who are also receiving medicinal products which are P-gp substrates (e.g. digoxin, quinidine).

*Potential medicinal product interactions affecting Zonisamide*

In clinical studies co-administration of lamotrigine had no apparent effect on zonisamide pharmacokinetics. The combination of Zonisamide with other medicinal products that may lead to urolithiasis may enhance the risk of developing kidney stones; therefore the concomitant administration of such medicinal products should be avoided.

Zonisamide is metabolised partly by CYP3A4 (reductive cleavage), and also by N-acetyl-transferases and conjugation with glucuronic acid; therefore, substances that can induce or inhibit these enzymes may affect the pharmacokinetics of zonisamide:

- Enzyme induction: Exposure to zonisamide is lower in epileptic patients receiving CYP3A4-inducing agents such as phenytoin, carbamazepine, and phenobarbitone. These effects are unlikely to be of clinical significance when Zonisamide is added to existing therapy; however, changes in zonisamide concentrations may occur if concomitant CYP3A4-inducing anti-epileptic or other medicinal products are withdrawn, dose adjusted or introduced, an adjustment of the Zonisamide dose may be required. Rifampicin is a potent CYP3A4 inducer. If co-administration is necessary, the patient should be closely monitored and the dose of Zonisamide and other CYP3A4 substrates adjusted as needed.

- CYP3A4 inhibition: Based upon clinical data, known specific and non-specific CYP3A4 inhibitors appear to have no clinically relevant effect on zonisamide pharmacokinetic exposure parameters. Steady-state dosing of either ketoconazole (400 mg/day) or cimetidine (1200 mg/day) had no clinically relevant effects on the single-dose pharmacokinetics of zonisamide given to healthy subjects. Therefore, modification of Zonisamide dosing should not be necessary when co-administered with known CYP3A4 inhibitors.

Paediatric population

Interaction studies have only been performed in adults.

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential must use effective contraception during treatment with Zonisamide, and for one month after discontinuation.

Zonisamide must not be used in women of childbearing potential not using effective contraception unless clearly necessary and only if the potential benefit is considered to justify the risk to the foetus. Specialist medical advice should be given to women treated with zonisamide who are of childbearing potential. The woman should be fully informed of and understand the possible effects of zonisamide on the foetus and these risks should be discussed with the patient in relation to the benefits before starting treatment. Pregnancy testing in women of childbearing potential should be considered prior to initiating treatment with zonisamide. Women planning a pregnancy should meet with their specialists to reassess treatment with zonisamide and to consider other therapeutic options prior to conception and before contraception is discontinued.

As with all antiepileptic medicines, sudden discontinuation of zonisamide should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child. The risk of birth defect is increased by factor 2 to 3 in the offspring of mothers treated with an antiepileptic

medicinal product. The most frequently reported are cleft lip, cardiovascular malformations and neural tube defect. Multiple antiepileptic medicinal product therapy may be associated with a higher risk of congenital malformations than monotherapy.

Pregnancy

There are limited data from the use of Zonisamide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). In humans he potential risk of major congenital malformations and neurodevelopmental disorders is unknown.

Data from a registry study suggest an increase in the proportion of babies born at a low birth weight (LBW), pre-term or small for gestational age (SGA). These increases are from about 5% to 8% for LBW, from about 8% to 10% for pre-term birth and from about 7% to 12% for SGA, all compared with mothers treated with lamotrigine monotherapy.

Zonisamide must not be used during pregnancy unless clearly necessary and only if the potential benefit is considered to justify the risk to the foetus. If Zonisamide is prescribed during pregnancy, patients should be fully informed of the potential harm to the foetus and use of the minimal effective dose is advised along with careful monitoring.

Breast-feeding

Zonisamide is excreted in human milk; the concentration in breast milk is similar to maternal plasma. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Zonisamide therapy. Due to the long retention time of zonisamide in the body, breast-feeding must not be resumed until one month after Zonisamide therapy is completed.

Fertility

There are no clinical data available on the effects of zonisamide on human fertility. Studies in animals have shown changes in fertility parameters (see section 5.3).

## 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, given that some patients may experience drowsiness or difficulty with concentration, particularly early in treatment or after a dose increase, patients must be advised to exercise caution during activities requiring a high degree of alertness, e.g., driving or operating machines.

## 4.8 Undesirable effects

Summary of the safety profile

Zonisamide has been administered to over 1,200 patients in clinical studies, more than 400 of whom received Zonisamide for at least 1 year. In addition there has been extensive post-marketing experience with zonisamide in Japan since 1989 and in the USA since 2000.

It should be noted that Zonisamide is a benzisoxazole derivative, which contains a sulphonamide group. Serious immune based adverse reactions that are associated with medicinal products containing a sulphonamide group include rash, allergic reaction and major haematological disturbances including aplastic anaemia, which very rarely can be fatal (see section 4.4).

The most common adverse reactions in controlled adjunctive-therapy studies were somnolence, dizziness and anorexia. The most common adverse reactions in a randomised, controlled monotherapy trial comparing zonisamide with carbamazepine prolonged release were decreased bicarbonate, decreased appetite, and decreased weight. The incidence of markedly abnormally low serum bicarbonate (a decrease to less than 17 mEq/l and by more than 5 mEq/l) was 3.8%. The incidence of marked decreases in weight of 20% or more was 0.7%.

Tabulated list of adverse reactions

Adverse reactions associated with Zonisamide obtained from clinical studies and post-marketing surveillance are tabulated below. The frequencies are arranged according to the following scheme:

| | |
|---|---|
| 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 |

**Table 4. Adverse reactions associated with Zonisamide obtained from adjunctive use clinical studies and post-marketing surveillance**

| **System Organ Class** (MedDRA terminology) | **Very Common** | **Common** | **Uncommon** | **Very Rare** |
|---|---|---|---|---|
| **Infections and infestation** | | | Pneumonia<br>Urinary tract infection | |
| **Blood and lymphatic system disorders** | | Ecchymosis | | Agranulocytosis<br>Aplastic anaemia<br>Leucocytosis<br>Leucopoenia<br>Lymphadenopathy<br>Pancytopenia,<br>Thrombocytopenia |
| **Immune system disorders** | | Hypersensitivity | | Drug-induced hypersensitivity syndrome<br>Drug rash with |

| | | | | |
|---|---|---|---|---|
| | | | | eosinophilia and systemic symptoms |
| **Metabolism and nutrition disorders** | Anorexia | | Hypokalaemia | Metabolic acidosis<br>Renal tubular acidosis |
| **Psychiatric Disorders** | Agitation<br>Irritability<br>Confusional state<br>Depression | Affect lability<br>Anxiety<br>Insomnia<br>Psychotic disorder | Anger<br>Aggression<br>Suicidal ideation<br>Suicide attempt | Hallucination |
| **Nervous system disorders** | Ataxia<br>Dizziness<br>Memory impairment<br>Somnolence | Bradyphrenia<br>Disturbance in attention<br>Nystagmus<br>Paraesthesia<br>Speech disorder<br>Tremor | Convulsion | Amnesia<br>Coma<br>Grand mal seizure<br>Myasthenic syndrome<br>Neuroleptic malignant syndrome<br>Status epilepticus |
| **Eye disorders** | Diplopia | | | Angle closure glaucoma<br>Eye pain<br>Myopia<br>Vision blurred<br>Visual acuity reduced |
| **Respiratory, thoracic and mediastinal disorders** | | | | Dyspnoea<br>Pneumonia aspiration<br>Respiratory disorder<br>Hypersensitivity-type Pneumonitis |
| **Gastrointestinal disorders** | | Abdominal pain<br>Constipation<br>Diarrhoea<br>Dyspepsia<br>Nausea | Vomiting | Pancreatitis |
| **Hepatobiliary disorders** | | | Cholecystitis<br>Cholelithiasis | Hepatocellular damage |
| **Skin and subcutaneous tissue disorders** | | Rash<br>Pruritus<br>Alopecia | | Anhidrosis<br>Erythema multiforme<br>Stevens-Johnson syndrome<br>Toxic epidermal necrolysis |
| **Musculoskeletal and connective tissue disorders** | | | | Rhabdomyolysis |
| **Renal and urinary disorders** | | Nephrolithiasis | Calculus urinary | Hydronephrosis<br>Renal failure<br>Urine abnormality |

| | | | | |
|---|---|---|---|---|
| **General disorders and administration site conditions** | | Fatigue<br>Influenza-like illness<br>Pyrexia<br>Oedema peripheral | | |
| **Investigations** | Decreased bicarbonate | Weight decreased | | Blood creatine phosphokinase increased<br>Blood creatinine increased<br>Blood urea increased<br>Liver function tests abnormal |
| **Injury, poisoning and procedural complications** | | | | Heat stroke |

In addition there have been isolated cases of Sudden Unexplained Death in Epilepsy Patients (SUDEP) receiving Zonisamide.

**Table 5. Adverse reactions in a randomised, controlled monotherapy trial comparing zonisamide with carbamazepine prolonged release**

| **System Organ Class** (MedDRA terminology†) | **Very Common** | **Common** | **Uncommon** |
|---|---|---|---|
| **Infections and infestation** | | | Urinary tract infection<br>Pneumonia |
| **Blood and lymphatic disorders** | | | Leukopenia<br>Thrombocytopenia |
| **Metabolism and nutrition disorders** | | Decreased appetite | Hypokalaemia |
| **Psychiatric Disorders** | | Agitation<br>Depression<br>Insomnia<br>Mood swings<br>Anxiety | Confusional state<br>Acute psychosis<br>Aggression<br>Suicidal ideation<br>Hallucination |
| **Nervous system disorders** | | Ataxia<br>Dizziness<br>Memory impairment<br>Somnolence<br>Bradyphrenia<br>Disturbance in attention<br>Paraesthesia | Nystagmus<br>Speech disorder<br>Tremor<br>Convulsion |
| **Eye disorders** | | Diplopia | |

| | | | |
|---|---|---|---|
| **Respiratory, thoracic and mediastinal disorders** | | | Respiratory disorder |
| **Gastrointestinal disorders** | | Constipation<br>Diarrhoea<br>Dyspepsia<br>Nausea<br>Vomiting | Abdominal pain |
| **Hepatobiliary disorders** | | | Cholecystitis acute |
| **Skin and subcutaneous tissue disorders** | | Rash | Pruritus<br>Ecchymosis |
| **General disorders and administration site conditions** | | Fatigue<br>Pyrexia<br>Irritability | |
| **Investigations** | Decreased bicarbonate | Weight decreased<br>Blood creatinine phosphokinase increased<br>Alanine aminotransferase increased<br>Aspartate aminotransferase increased | Urine analysis abnormal |

† MedDRA version 13.1

Additional information on special populations:

*Elderly*

A pooled analysis of safety data on 95 elderly subjects has shown a relatively higher reporting frequency of oedema peripheral and pruritus compared to the adult population.

Review of post-marketing data suggests that patients aged 65 years or older report a higher frequency than the general population of the following events: Stevens-Johnson syndrome (SJS) and Drug Induced Hypersensitivity syndrome (DIHS).

*Paediatric population*

The adverse event profile of zonisamide in paediatric patients aged 6 to 17 years in placebo-controlled clinical studies was consistent with that of adults. Among 465 subjects in the paediatric safety database (including a further 67 subjects from the extension phase of the controlled clinical trial) there were 7 deaths (1.5%; 14.6/1000 person-years): 2 cases of status epilepticus, of which one was related to severe weight loss (10% within 3 months) in an underweight subject and subsequent failure to take medication; 1 case of head injury/haematoma, and 4 deaths in subjects with pre-existing functional neurological deficits for various causes (2 cases of pneumonia-induced sepsis/organ failure, 1 SUDEP and 1 head injury). A total of 70.4% of paediatric subjects who received ZNS in the controlled study or its open label extension had at least one treatment-emergent bicarbonate measurement below 22 mmol/L. The duration of low bicarbonate measurements was also long (median 188 days).

A pooled analysis of safety data on 420 paediatric subjects (183 subjects aged 6 to 11 years, and 237 subjects aged 12 to 16 years with a mean duration of exposure of approximately 12 months) has shown a relatively higher reporting frequency of

pneumonia, dehydration, decreased sweating, abnormal liver function tests, otitis media, pharyngitis, sinusitis and upper respiratory tract infection, cough, epistaxis and rhinitis, abdominal pain, vomiting, rash and eczema, and fever compared to the adult population (particularly in subjects aged below 12 years) and, at a low incidence, amnesia, creatinine increased, lymphadenopathy, and thrombocytopenia**.** The incidence of a decrease in body weight of 10% or more was 10.7% (see section 4.4). In some cases of weight decrease there was a delay in transition to the next Tanner stage and in bone maturation.

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: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

### 4.9 Overdose

There have been cases of accidental and intentional overdose in adult and paediatric patients. In some cases, the overdoses were asymptomatic, particularly where emesis or lavage was prompt. In other cases, the overdose was followed by symptoms such as somnolence, nausea, gastritis, nystagmus, myoclonus, coma, bradycardia, reduced renal function, hypotension and respiratory depression. A very high plasma concentration of 100.1 μg/ml zonisamide was recorded approximately 31 hours after a patient took an overdose of Zonisamide and clonazepam; the patient became comatose and had respiratory depression but recovered consciousness five days later and had no sequelae.

*Treatment*

No specific antidotes for Zonisamide overdose are available. Following a suspected recent overdose, emptying the stomach by gastric lavage or by induction of emesis may be indicated with the usual precautions to protect the airway. General supportive care is indicated, including frequent monitoring of vital signs and close observation. Zonisamide has a long elimination half-life so its effects may be persistent. Although not formally studied for the treatment of overdose, haemodialysis reduced plasma concentrations of zonisamide in a patient with reduced renal function and may be considered as treatment of overdose if clinically indicated.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, other antiepileptics, ATC code: N03AX15

Zonisamide is a benzisoxazole derivative. It is an anti-epileptic medicine with weak carbonic anhydrase activity *in-vitro*. It is chemically unrelated to other anti-epileptic agents.

Mechanism of action

The mechanism of action of zonisamide is not fully elucidated, but it appears to act on voltage-sensitive sodium and calcium channels, thereby disrupting synchronised neuronal firing, reducing the spread of seizure discharges and disrupting subsequent epileptic activity. Zonisamide also has a modulatory effect on GABA-mediated neuronal inhibition.

Pharmacodynamic effects

The anticonvulsant activity of zonisamide has been evaluated in a variety of models, in several species with induced or innate seizures, and zonisamide appears to act as a broad-spectrum anti-epileptic in these models. Zonisamide prevents maximal electroshock seizures and restricts seizure spread, including the propagation of seizures from cortex to sub-cortical structures and suppresses epileptogenic focus activity. Unlike phenytoin and carbamazepine however, zonisamide acts preferentially on seizures originating in the cortex.

Clinical efficacy and safety

*Monotherapy in partial seizures, with or without secondary generalisation*

Efficacy of zonisamide as monotherapy was established in a double-blind, parallel group, non-inferiority comparison to carbamazepine prolonged release (PR) in 583 adult subjects with newly diagnosed partial seizures with or without secondary generalised tonic-clonic seizures. Subjects were randomised to carbamazepine and zonisamide received treatment for a duration of up to 24 months depending on response. Subjects were titrated to the initial target dose of 600 mg carbamazepine or 300 mg of zonisamide. Subjects who experienced a seizure were titrated to the next target dose i.e. 800 mg carbamazepine or 400 mg of zonisamide. Subjects who experienced a further seizure were titrated to the maximal target dose of 1200 mg carbamazepine or 500 mg zonisamide. Subjects who were seizure-free for 26 weeks at a target dose level continued on this dose for another 26 weeks.

Main outcomes of this study are presented in this table:

**Table 6. Efficacy results for Monotherapy Study 310**

| | **Zonisamide** | **Carbamazepine** | | |
|---|---|---|---|---|
| n (ITT population) | 281 | 300 | | |
| **Six months seizure freedom** | | | Diff | $CI_{95\%}$ |
| PP-population* | 79.4% | 83.7% | -4.5% | -12.2% ; 3.1% |
| ITT-population | 69.4% | 74.7% | -6.1% | -13.6% ; 1.4% |
| ≤ 4 seizures during 3 month baseline period | 71.7% | 75.7% | -4.0% | -11.7% ; 3.7% |
| > 4 seizures during 3 month baseline period | 52.9% | 68.9% | -15.9% | -37.5% ; 5.6% |
| **Twelve months seizure freedom** | | | | |
| PP-population | 67.6% | 74.7% | -7.9% | - 17.2% ; 1.5% |
| ITT-population | 55.9% | 62.3% | -7.7% | - 16.1% ; 0.7% |

| | | | | |
|---|---|---|---|---|
| ≤ 4 seizures during 3 month baseline period | 57.4% | 64.7% | -7.2% | -15.7% ; 1.3% |
| > 4 seizures during 3 month baseline period | 44.1% | 48.9% | -4.8% | -26.9% ; 17.4% |
| **Seizure Sub-type (6 month seizure freedom-PP population)** | | | | |
| All partial | 76.4% | 86.0% | -9.6% | -19.2% ; 0.0% |
| Simple partial | 72.3% | 75.0% | -2.7% | -20.0% ; 14.7% |
| Complex partial | 76.9% | 93.0% | -16.1% | -26.3% ; -5.9% |
| All generalized Tonic-Clonic | 78.9% | 81.6% | -2.8% | -11.5% ; 6.0% |
| Secondary Tonic-Clonic | 77.4% | 80.0% | -2.6% | -12.4% ; 7.1% |
| Generalized Tonic-Clonic | 85.7% | 92.0% | -6.3% | -23.1% ; 10.5% |

PP = Per Protocol Population; ITT = Intent To Treat Population

*Primary endpoint

*Adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation in adults*

In adults, efficacy has been demonstrated with Zonisamide in 4 double-blind, placebo-controlled studies of periods of up to 24 weeks with either once or twice daily dosing. These studies show that the median reduction in partial seizure frequency is related to Zonisamide dose with sustained efficacy at doses of 300-500 mg per day.

Paediatric population

*Adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation, in adolescent and paediatric patients (aged 6 years and above)*

In paediatric patients (aged 6 years and above), efficacy has been demonstrated with zonisamide in a double-blind, placebo-controlled study, which included 207 subjects and had a treatment duration of up to 24 weeks. A 50% or greater reduction from baseline in seizure frequency during the 12-week stable dose period was seen in 50% of the zonisamide-treated subjects and 31% of the patients on placebo.

Specific safety issues that were encountered in the paediatric studies were: decreased appetite and weight loss, decreased bicarbonate levels, increased risk of kidney stones and dehydration. All these effects and specifically weight loss may have deleterious implications for growth and development and may lead to general deterioration of health. Altogether, data on effects on long-term growth and development are limited.

## 5.2 Pharmacokinetic properties

*Absorption*

Zonisamide is almost completely absorbed after oral administration, generally reaching peak serum or plasma concentrations within 2 to 5 hours of dosing. The first-pass metabolism is believed to be negligible. Absolute bioavailability is estimated to be approximately 100%. Oral bioavailability is not affected by food, although peak plasma and serum concentrations may be delayed.

Zonisamide AUC and $C_{max}$ values increased almost linearly after single dose over the dose range of 100-800 mg and after multiple doses over the dose range of 100-400 mg once daily. The increase at steady state was slightly more than expected on the basis of dose, probably due to the saturable binding of zonisamide to erythrocytes. Steady state was achieved within 13 days. Slightly greater than expected accumulation occurs relative to single dosing.

*Distribution*

Zonisamide is 40 - 50 % bound to human plasma proteins, with *in vitro* studies showing that this is unaffected by the presence of various antiepileptic medicinal products (i.e., phenytoin, phenobarbitone, carbamazepine, and sodium valproate). The apparent volume of distribution is about 1.1 – 1.7 l/kg in adults indicating that zonisamide is extensively distributed to tissues. Erythrocyte/plasma ratios are about 15 at low concentrations and about 3 at higher concentrations.

*Biotransformation*

Zonisamide is metabolised primarily through reductive cleavage of the benzisoxazole ring of the parent drug by CYP3A4 to form 2-sulphamoylacetylphenol (SMAP) and also by N-acetylation. Parent drug and SMAP can additionally be glucuronidated. The metabolites, which could not be detected in plasma, are devoid of anticonvulsant activity. There is no evidence that zonisamide induces its own metabolism.

*Elimination*

Apparent clearance of zonisamide at steady-state after oral administration is about 0.70 l/h and the terminal elimination half-life is about 60 hours in the absence of CYP3A4 inducers. The elimination half-life was independent of dose and not affected by repeat administration. Fluctuation in serum or plasma concentrations over a dosing interval is low (< 30 %). The main route of excretion of zonisamide metabolites and unchanged drug is via the urine. Renal clearance of unchanged zonisamide is relatively low (approximately 3.5 ml/min); about 15 - 30 % of the dose is eliminated unchanged.

Linearity/non-linearity

Zonisamide exposure increases with time until steady state is achieved by approximately 8 weeks. When comparing the same dose level, subjects of higher total body weight appear to have lower steady-state serum concentrations, but this effect appears to be relatively modest. Age (≥ 12 years) and gender, after adjustment for body weight effects, have no apparent effect on zonisamide exposure in epileptic patients during steady-state dosing. There is no need for dose adjustment with any of the AEDs including CYP3A4 inducers.

Pharmacokinetic/pharmacodynamic relationship

Zonisamide lowers the 28-day average seizure frequency and the decrease is proportional (log-linear) to zonisamide average concentration.

*Special patient groups*

*In subjects with renal impairment*, renal clearance of single doses of zonisamide was positively correlated with creatinine clearance. The plasma AUC of zonisamide was increased by 35% in subjects with creatinine clearance <20 ml/min (see also section 4.2.).

*Patients with an impaired liver function:* The pharmacokinetics of zonisamide in patients with impaired liver function have not been adequately studied.

*Elderly:* No clinically significant differences were observed in the pharmacokinetics between young (aged 21-40 years) and elderly (65-75 years).

*Children and adolescents (5-18 years):* Limited data indicate that pharmacokinetics in children and adolescents dosed to steady state at 1, 7 or 12 mg/kg daily, in divided doses, are similar to those observed in adults, after adjustment for bodyweight.

### 5.3 Preclinical safety data

Findings not observed in clinical studies but seen in the dog at exposure levels similar to clinical use, were liver changes (enlargement, dark-brown discolouration, mild hepatocyte enlargement with concentric lamellar bodies in the cytoplasm and cytoplasmic vacuolation) associated with increased metabolism.

Zonisamide was not genotoxic and has no carcinogenic potential.

Zonisamide was embryotoxic and teratogenic (reduced pup weight, increase in cardiac and major blood vessel defects, delayed ossification) in mice, rats and dogs and induced maternal toxicity at high doses. In monkeys zonisamide acted as an abortifacient at all doses tested and given the embryolethality a teratogenic potential in monkeys cannot be ruled out.

Zonisamide also causes a reduction in food consumption, reduced maternal and fetal bodyweight gain and a reduction in growth parameters in the fetus (small for gestational weight). The plasma concentrations associated with the embryotoxicity was within the therapeutic range.

In a repeated-dose oral toxicity study in juvenile rats, at exposure levels similar to those observed in paediatric patients at the maximum recommended dose, decreases in body weight and changes in renal histopathology and clinical pathology parameters and behavioural changes were observed. Changes in renal histopathology and clinical pathology parameters were considered to be related to carbonic anhydrase inhibition by zonisamide. The effects at this dose level were reversible during the recovery period. At a higher dose level (2-3-fold systemic exposure compared to therapeutic exposure) renal histopathological effects were more severe and only partially reversible. Most adverse effects observed in the juvenile rats were similar to those seen in the repeated-dose toxicity studies of zonisamide in adult rats, but renal tubular hyaline droplets and transitional hyperplasia were observed in the juvenile study only. At this higher dose level, juvenile rats showed a decrease in growth, learning, and developmental parameters. These effects were considered likely related to the decreased body weight and exaggerated pharmacologic effects of zonisamide at the maximum tolerated dose.

In rats, decreased numbers of corpora lutea and implantation sites were observed at exposure levels equivalent to the maximum therapeutic dose in humans; irregular oestrus cycles and a decreased number of live foetuses were observed at exposure levels three times higher.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Capsule contents

Cellulose, Microcrystalline (Grade-101)
Cellulose, Microcrystalline (Grade-102)
Macrogol glycerol hydroxy stearate
Hydrogenated vegetable oil

Capsule shell

Titanium dioxide
Gelatin
Iron oxide Red (E172)

Black Ink

Shellac (E904)
Black iron oxide (E172)
Potassium hydroxide (E525)

## 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

Clear PVC/PVdC - Aluminium foil blister

Pack sizes 56 hard capsules.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7 MARKETING AUTHORISATION HOLDER

Milpharm Limited
Ares Block,
Odyssey Business Park,
West End Road,
Ruislip, HA4 6QD
United Kingdom

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 16363/0721

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/12/2022

## 10 DATE OF REVISION OF THE TEXT

29/04/2024