ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zonisamide Viatris 25 mg hard capsules
Zonisamide Viatris 50 mg hard capsules
Zonisamide Viatris 100 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Zonisamide Viatris 25 mg hard capsules

Each hard capsule contains 25 mg of zonisamide.

Zonisamide Viatris 50 mg hard capsules

Each hard capsule contains 50 mg of zonisamide.

Zonisamide Viatris 100 mg hard capsules

Each hard capsule contains 100 mg of zonisamide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Zonisamide Viatris 25 mg hard capsules

A white opaque body and a white opaque cap, marked ‘Z 25’ in black containing white/almost white powder. Each hard capsule is approximately 14.4 mm in length.

Zonisamide Viatris 50 mg hard capsules

A white opaque body and a white opaque cap, marked ‘Z 50’ in red containing white/almost white powder. Each hard capsule is approximately 15.8 mm in length.

Zonisamide Viatris 100 mg hard capsules

A white opaque body and a white opaque cap, marked ‘Z 100’ in black containing white/almost white powder. Each hard capsule is approximately 19.3 mm in length.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zonisamide Viatris 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 Viatris 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When Zonisamide Viatris treatment is to be discontinued, it should be withdrawn gradually (see section 4.4).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). 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 - with CYP3A4-inducing agents (see section 4.5)	**Week 1**	**Week 2**	**Week 3 to 5**	300 to 500 mg per day (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-inducing agents; or with renal or hepatic impairment	**Week 1 + 2**	**Week 3 + 4**	**Week 5 to 10**	300 to 500 mg per day (once a day or two divided doses). Some patients may respond to lower doses.
	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	

General dosing recommendations for Zonisamide Viatris in special patient populations

Paediatric population (aged 6 years and above)

Dosage escalation and maintenance
Zonisamide Viatris 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 heat stroke (see section 4.4: Paediatric Population).

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

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

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 55 kg. 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).

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 Viatris 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.

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 Viatris may be required.

Method of administration
Zonisamide Viatris hard capsules are for oral use.

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

4.3 Contraindications

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

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.

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

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

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 Viatris 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 the 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 sulfonamide group. Serious immune based adverse reactions that are associated with medicinal products containing a sulfonamide 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 Urinary tract infection	
Blood and lymphatic system disorders		Ecchymosis		Agranulocytosis Aplastic anaemia Leucocytosis Leucopoenia Lymphadenopathy Pancytopenia, Thrombocytopenia
Immune system disorders		Hypersensitivity		Drug-induced hypersensitivity syndrome Drug rash with eosinophilia and systemic symptoms
Metabolism and nutrition disorders	Anorexia		Hypokalaemia	Metabolic acidosis Renal tubular acidosis
Psychiatric Disorders	Agitation Irritability Confusional state Depression	Affect lability Anxiety Insomnia Psychotic disorder	Anger Aggression Suicidal ideation Suicide attempt	Hallucination
Nervous system disorders	Ataxia Dizziness Memory impairment Somnolence	Bradyphrenia Disturbance in attention Nystagmus Paraesthesia Speech disorder Tremor	Convulsion	Amnesia Coma Grand mal seizure Myasthenic syndrome Neuroleptic malignant syndrome Status epilepticus

System Organ Class (MedDRA terminology)	**Very Common**	**Common**	**Uncommon**	**Very Rare**
Eye disorders	Diplopia			Angle closure glaucoma Eye pain Myopia Vision blurred Visual acuity reduced
Respiratory, thoracic and mediastinal disorders				Dyspnoea Pneumonia aspiration Respiratory disorder Hypersensitivity-type Pneumonitis
Gastrointestinal disorders		Abdominal pain Constipation Diarrhoea Dyspepsia Nausea	Vomiting	Pancreatitis
Hepatobiliary disorders			Cholecystitis Cholelithiasis	Hepatocellular damage
Skin and subcutaneous tissue disorders		Rash Pruritus Alopecia		Anhidrosis Erythema multiforme Stevens-Johnson syndrome Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders				Rhabdomyolysis
Renal and urinary disorders		Nephrolithiasis	Calculus urinary	Hydronephrosis Renal failure Urine abnormality
General disorders and administration site conditions		Fatigue Influenza-like illness Pyrexia Oedema peripheral		
Investigations	Decreased bicarbonate	Weight decreased		Blood creatine phosphokinase increased Blood creatinine increased Blood urea increased 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 Pneumonia
Blood and lymphatic disorders			Leucopenia Thrombocytopenia
Metabolism and nutrition disorders		Decreased appetite	Hypokalaemia
Psychiatric Disorders		Agitation Depression Insomnia Mood swings Anxiety	Confusional state Acute psychosis Aggression Suicidal ideation Hallucination
Nervous system disorders		Ataxia Dizziness Memory impairment Somnolence Bradyphrenia Disturbance in attention Paraesthesia	Nystagmus Speech disorder Tremor Convulsion
Eye disorders		Diplopia	
Respiratory, thoracic and mediastinal disorders			Respiratory disorder
Gastrointestinal disorders		Constipation Diarrhoea Dyspepsia Nausea Vomiting	Abdominal pain
Hepatobiliary disorders			Cholecystitis acute
Skin and subcutaneous tissue disorders		Rash	Pruritus Ecchymosis
General disorders and administration site conditions		Fatigue Pyrexia Irritability	
Investigations	Decreased bicarbonate	Weight decreased Blood creatinine phosphokinase increased Alanine aminotransferase increased 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 national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
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.

Management
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-sulfamoylacetylphenol (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

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.).

Hepatic impairment
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 caused developmental abnormalities in mice, rats, and dogs, and was embryolethal in monkeys, when administered during the period of organogenesis at zonisamide dosage and maternal plasma levels similar to or lower than therapeutic levels in humans.

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

Zonisamide Viatris 25 mg and 100 mg hard capsules

Capsule contents
Microcrystalline cellulose
Sodium laurilsulfate
Hydrogenated vegetable oil

Capsule shells
Titanium dioxide (E171)
Gelatin

Printing ink
Shellac
Black iron oxide (E172)
Potassium hydroxide

Zonisamide Viatris 50 mg hard capsules

Capsule contents
Microcrystalline cellulose
Sodium laurilsulfate
Hydrogenated vegetable oil

Capsule shells
Titanium dioxide (E171)

Gelatin

Printing ink
Shellac
Iron oxide Red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Zonisamide Viatris 25 mg and 50 mg hard capsules

PVC-PVdC/Aluminium foil blisters in cardboard cartons containing 14, 28 and 56 capsules.
PVC-PVdC/Aluminium foil perforated unit dose blisters in cardboard cartons containing 14 x 1 capsules.

Zonisamide Viatris 100 mg hard capsules

PVC-PVdC/Aluminium foil blisters in cardboard cartons containing 28, 56, 98 and 196 capsules.
PVC-PVdC/Aluminium foil perforated unit dose blisters in cardboard cartons containing 56 x 1 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

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

7. MARKETING AUTHORISATION HOLDER

Viatris Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

Zonisamide Viatris 25 mg hard capsules

EU/1/16/1093/001
EU/1/16/1093/002
EU/1/16/1093/003
EU/1/16/1093/004

Zonisamide Viatris 50 mg hard capsules

EU/1/16/1093/005
EU/1/16/1093/006
EU/1/16/1093/007
EU/1/16/1093/008

Zonisamide Viatris 100 mg hard capsules

EU/1/16/1093/009
EU/1/16/1093/010
EU/1/16/1093/011
EU/1/16/1093/012
EU/1/16/1093/013

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 March 2016
Date of latest renewal: 01 December 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency: http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Noucor Health, S.A.
Av. Camí Reial, 51-57
ES-08184 – Palau-solità i Plegamans
Barcelona
Spain

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Zonisamide Viatris 25 mg hard capsules
zonisamide

2. STATEMENT OF ACTIVE SUBSTANCE

Each hard capsule contains 25 mg zonisamide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsules

Blisters:
14 hard capsules
28 hard capsules
56 hard capsules

Unit Dose Blisters:
14 x 1 hard capsules

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/16/1093/001
EU/1/16/1093/002
EU/1/16/1093/003
EU/1/16/1093/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS FOR USE

16. INFORMATION IN BRAILLE

Zonisamide Viatris 25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER PACK

1. NAME OF THE MEDICINAL PRODUCT

Zonisamide Viatris 25 mg hard capsules
zonisamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Viatris Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Zonisamide Viatris 50 mg hard capsules.
zonisamide

2. STATEMENT OF ACTIVE SUBSTANCE

Each hard capsule contains 50 mg zonisamide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsules

Blisters:
14 hard capsules
28 hard capsules
56 hard capsules

Unit Dose Blisters:
14 x 1 hard capsules

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/16/1093/005
EU/1/16/1093/006
EU/1/16/1093/007
EU/1/16/1093/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS FOR USE

16. INFORMATION IN BRAILLE

Zonisamide Viatris 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER PACK

1. NAME OF THE MEDICINAL PRODUCT

Zonisamide Viatris 50 mg hard capsules
zonisamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Viatris Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Zonisamide Viatris 100 mg hard capsules.
zonisamide

2. STATEMENT OF ACTIVE SUBSTANCE

Each hard capsule contains 100 mg zonisamide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsules

Blisters:
28 hard capsules
56 hard capsules
98 hard capsules
196 hard capsules

Unit Dose Blisters:
56 x 1 hard capsules

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/16/1093/009
EU/1/16/1093/010
EU/1/16/1093/011
EU/1/16/1093/012
EU/1/16/1093/013

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS FOR USE

16. INFORMATION IN BRAILLE

Zonisamide Viatris 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN

NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER PACK

1. NAME OF THE MEDICINAL PRODUCT

Zonisamide Viatris 100 mg hard capsules
zonisamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Viatris Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Zonisamide Viatris 25 mg hard capsules
Zonisamide Viatris 50 mg hard capsules
Zonisamide Viatris 100 mg hard capsules
zonisamide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Zonisamide Viatris is and what it is used for

Zonisamide Viatris contains the active substance zonisamide, and is used as an antiepileptic medicine.

Zonisamide Viatris is used to treat seizures that affect one part of the brain (partial seizure), which may or may not be followed by a seizure affecting all of the brain (secondary generalisation).

Zonisamide Viatris may be used:
- on its own to treat seizures in adults
- with other antiepileptic medicines to treat seizures in adults, adolescents, and children aged 6 years and above.

2. What you need to know before you take Zonisamide Viatris

Do not take Zonisamide Viatris
- if you are allergic to zonisamide or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to other sulfonamide medicines. Examples include: sulfonamide antibiotics, thiazide diuretics, and sulfonylurea antidiabetes medicines.

Warnings and precautions
Zonisamide Viatris belongs to a group of medicines (sulfonamides) which can cause severe allergic reactions, severe skin rashes, and blood disorders, which very rarely can be fatal (see section 4. Possible Side Effects).

A small number of people being treated with antiepileptics such as zonisamide have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

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

The use of Zonisamide Viatris may lead to high levels of ammonia in the blood which could lead to a change in brain function, especially if you are also taking other medicines which can increase ammonia

levels (for example valproate), have a genetic disorder causing build-up of too much ammonia in the body (urea cycle disorder), or if you have liver problems. Tell your doctor immediately if you become unusually drowsy or confused.

Talk to your doctor or pharmacist before taking Zonisamide Viatris if you:
- are younger than 12 years old, as you may be at greater risk of decreased sweating, heat stroke, pneumonia and liver problems. If you are younger than 6 years old, Zonisamide Viatris is not recommended for you
- are elderly, as your dose of Zonisamide Viatris may need adjusting, and you may be more likely to develop an allergic reaction, severe skin rash, swelling of the feet and legs, and itchiness when taking Zonisamide Viatris (see section 4 Possible Side Effects)
- suffer from liver problems, as your dose of Zonisamide Viatris may need adjusting
- have eye problems such as glaucoma
- suffer from kidney problems as your dose of Zonisamide Viatris may need adjusting
- have previously suffered from kidney stones, as you may be at increased risk of developing more kidney stones. **Reduce the risk of kidney stones by drinking sufficient water**
- live in a place or are on holiday in a place where the weather is warm. Zonisamide Viatris can make you perspire less, which can cause your body temperature to increase. **Reduce the risk of overheating by drinking sufficient water and keeping cool**
- are underweight, or have lost a lot of weight as Zonisamide Viatris can cause you to lose more weight. Tell your doctor as this may need to be monitored.
- are pregnant or could become pregnant (see section 'pregnancy, breast-feeding and fertility' for further information).

If any of these applies to you, tell your doctor before you take Zonisamide Viatris.

Children and adolescents
Talk to your doctor about the following risks:

Preventing overheating and dehydration in children

Zonisamide Viatris can cause your child to sweat less and overheat and if your child is not treated this can lead to brain damage and death. Children are most at risk especially in hot weather.

When your child is taking Zonisamide Viatris:
- keep your child cool especially in hot weather
- your child must avoid heavy exercise especially when the weather is hot
- give your child plenty of cold water to drink
- your child must not take these medicines:

carbonic anhydrase inhibitors (like topiramate and acetazolamide), and anticholinergic agents (like clomipramine, hydroxyzine, diphenhydramine, haloperidol, imipramine and oxybutynin).

If your child's skin feels very hot with little or no sweating, becomes confused, has muscle cramps, or your child's heartbeat or breathing becomes rapid:
- take your child to a cool, shaded place
- sponge your child's skin with cool (not cold) water
- give your child cold water to drink
- seek urgent medical assistance.

- Body weight: You should monitor your child's weight every month and see your doctor as soon as possible if your child is not gaining enough weight. Zonisamide Viatris is not recommended for children who are underweight or have a small appetite, and should be used with caution in those below 20 kg.
- Increased acid level in the blood and kidney stones: Reduce these risks by ensuring that your child drinks enough water and is not taking any other medicine which could cause kidney stones (see Other medicines). Your doctor will monitor your child's blood bicarbonate levels and kidneys

(see also section 4).

Do not give this medicine to children below the age of 6 years because it is not known for this age group whether the potential benefits are greater than the risks.

Other medicines and Zonisamide Viatris
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.
- Zonisamide Viatris should be used carefully in adults when taken with medicines that can cause kidney stones, like topiramate or acetazolamide. In children, this combination is not recommended.
- Zonisamide Viatris could possibly increase your blood levels of medicines like digoxin and quinidine, and so a reduction in their dose may be required.
- Other medicines like phenytoin, carbamazepine, phenobarbitone and rifampicin can decrease your blood levels of Zonisamide Viatris, which may require an adjustment of your dose of Zonisamide Viatris.

Zonisamide Viatris with food and drink
Zonisamide Viatris can be taken with or without food.

Pregnancy, breast-feeding and fertility
If you are a woman of childbearing age you must use adequate contraception while taking, and for one month after stopping, Zonisamide Viatris.

If you are planning a pregnancy, talk to your doctor before you stop contraception and before you become pregnant about the possibility of switching to other suitable treatments. If you are or think you might be pregnant, tell your doctor straight away. You should not stop your treatment without discussing this with your doctor.

You must only take Zonisamide Viatris during your pregnancy if your doctor tells you to. Research has shown an increased risk of birth defects in children of women taking anti-epileptic medicines. The risk of birth defects or neurodevelopmental disorders (problems with brain development) for your child after taking Zonisamide Viatris during your pregnancy is unknown. A study showed that babies born to mothers using zonisamide during pregnancy were smaller than expected for their age at birth, compared with babies born to mothers treated with lamotrigine monotherapy. Make sure you are fully informed about the risks and the benefits of using zonisamide for epilepsy during pregnancy.

Do not breast-feed whilst taking, or for one month after stopping Zonisamide Viatris.

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

Driving and using machines
Zonisamide Viatris may affect your concentration, ability to react/respond, and may make you feel sleepy, particularly at the beginning of your treatment or after your dose is increased. Be especially careful while driving or operating machinery if Zonisamide Viatris affects you in this way.

Zonisamide Viatris contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially ‘sodium-free’.

3. How to take Zonisamide Viatris

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended adult dose

When you take Zonisamide Viatris on its own:
- The starting dose is 100 mg taken once a day.
- This may be increased by up to 100 mg at intervals of two weeks.
- The recommended dose is 300 mg once a day.

When you take Zonisamide Viatris with other antiepileptic medicines:
- The starting dose is 50 mg daily taken in two equal doses of 25 mg.
- This may be increased by up to 100 mg at intervals of one to two weeks.
- The recommended daily dose is between 300 mg and 500 mg.
- Some people respond to lower doses. The dose may be increased more slowly if you experience side effects, are elderly or if you suffer from kidney or liver problems.

Use in children (aged 6 to 11 years) and adolescents (aged 12 to 17 years) weighing at least 20 kg:
- The starting dose is 1 mg per kg of body weight taken once a day.
- This may be increased by 1 mg per kg of body weight at intervals of one to two weeks.
- The recommended daily dose is 6 to 8 mg per kg for a child with a body weight of up to 55 kg or 300 to 500 mg for a child with a body weight more than 55 kg (which ever dose is lower) taken once a day.

Example: A child who weighs 25 kg should take 25 mg once a day for the first week, and then increase the daily dose by 25 mg at the start of each week until a daily dose between 150 to 200 mg is reached.

If you feel that the effect of Zonisamide Viatris is too strong or too weak, talk to your doctor or pharmacist.

- Zonisamide Viatris capsules must be swallowed whole with water.
- Do not chew the capsules.
- Zonisamide Viatris can be taken once or twice daily, as instructed by your doctor.
- If you take Zonisamide Viatris twice a day, take half the daily dose in the morning and half in the evening.

If you take more Zonisamide Viatris than you should
If you may have taken more Zonisamide Viatris than you should, tell a carer (relative or friend), your doctor or pharmacist immediately, or contact your nearest hospital casualty department, taking your medicine with you. You may become sleepy and could lose consciousness. You might also feel sick, have a sore stomach, muscle twitches, eye movement, feel faint, have a slowed heartbeat, and reduced breathing and kidney function. Do not try to drive.

If you forget to take Zonisamide Viatris
- If you forget to take a dose, don't worry: take the next dose when it is due.
- Do not take a double dose to make up for a forgotten dose.

If you stop taking Zonisamide Viatris
- Zonisamide Viatris is meant to be taken as a long-term medicine. Do not reduce your dose or stop your medicine unless your doctor tells you to.
- If your doctor advises you to stop taking Zonisamide Viatris your dose will be reduced gradually to lower the risk of more seizures.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Zonisamide Viatris belongs to a group of medicines (sulfonamides) that can cause severe allergic reactions, severe skin rashes, and blood disorders, which very rarely can be fatal.

Contact your doctor immediately if you:
- have difficulty breathing, a swollen face, lips or tongue, or a severe skin rash as these symptoms may indicate that you are having a severe allergic reaction
- have signs of overheating - high body temperature but little or no sweating, rapid heartbeat and breathing, muscle cramps, and confusion
- have thoughts of harming or killing yourself. A small number of people being treated with anti-epileptics such as Zonisamide Viatris have had thoughts of harming or killing themselves
- have pain in your muscles or a feeling of weakness, as this may be a sign of abnormal muscle breakdown which can lead to kidney problems
- get a sudden pain in your back or stomach, have pain on urinating (passing water) or notice blood in your urine, as this may be a sign of kidney stones
- develop visual problems such as eye pain or blurred vision while taken zonisamide.

Contact your doctor as soon as possible if you:
- have an unexplained skin rash, as this could develop into a more severe skin rash or skin peeling
- feel unusually tired or feverish, have a sore throat, swollen glands, or find that you bruise more easily, as this may mean you have a blood disorder
- have signs of increased acid level in the blood- headaches, drowsiness, shortness of breath and loss of appetite. Your doctor may need to monitor or treat this.

Your doctor may decide that you should stop using Zonisamide Viatris.

The most common side effects of Zonisamide Viatris are mild. They occur during the first month of treatment and usually decrease with continued treatment. In children ages 6 – 17 years old, side effects were consistent with those described below with the following exceptions: pneumonia, dehydration, sweating decreased (common), abnormal liver enzymes (uncommon), middle ear infection, sore throat, sinus and chest infections, cough, nosebleeds, runny nose, stomach pain, vomiting, rash, eczema and fever.

Very common (may affect more than 1 in 10 people):
- agitation, irritability, confusion, depression
- poor muscle coordination, dizziness, poor memory, sleepiness, double vision
- loss of appetite, decreased blood levels of bicarbonate (a substance that prevents your blood from becoming acidic).

Common (may affect up to 1 in 10 people):
- difficulty sleeping, strange or unusual thoughts, feeling anxious or emotional
- slowed thoughts, loss of concentration, speech abnormalities, abnormal skin sensation (pins and needles), tremor, involuntary movement of the eyes
- kidney stones
- skin rashes, itching, allergic reactions, fever, tiredness, flu-like symptoms, hair loss
- ecchymosis (a small bruise caused by blood leaking from broken blood vessels in the skin)
- loss of weight, nausea, indigestion, stomach pains, diarrhoea (loose stools), constipation
- swelling of the feet and legs
- vomiting
- mood swings
- increased blood levels of creatinine (a waste product that your kidneys should normally remove)
- increased levels of liver enzymes in the blood.

Uncommon (may affect up to 1 in 100 people):
- anger, aggression, thoughts of suicide, suicide attempt
- gall bladder inflammation, gallstones
- urinary stones
- lung infection / inflammation, urinary tract infections

- low blood potassium levels, convulsions/seizures
- breathing disorders
- hallucinations
- abnormal urine tests.

Very rare (may affect up to 1 in 10,000 people):
- memory loss, coma, neuroleptic malignant syndrome (inability to move, sweating, fever, incontinence), status epilepticus (prolonged or repeated seizures)
- shortness of breath, inflammation of the lungs
- inflammations of the pancreas (severe pain in the stomach or back)
- liver problems, kidney failure
- severe rashes or skin peeling (at the same time you may feel unwell or develop a fever)
- abnormal muscle breakdown (you may feel pain or weakness in your muscles) which can lead to kidney problems
- swollen glands, blood disorders (reduction in the number of blood cells, which can make infection more likely and can make you look pale, feel tired and feverish, and bruise more easily)
- decreased sweating, overheating
- problems with your urine
- increased blood levels of creatine phosphokinase or urea which can be seen in a blood test
- abnormal results from liver function tests
- glaucoma, which is a blockage of fluid in the eye causing increased pressure in the eye. Eye pain, blurred vision or decreased vision may occur and can be signs of glaucoma.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Zonisamide Viatris

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

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

This medicine does not require any special storage conditions.

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

6. Contents of the pack and other information

What Zonisamide Viatris contains:

Zonisamide 25 mg hard capsules:
The active substance is zonisamide. Each capsule contains 25 mg of zonisamide.
The other ingredients are:
- capsule contents: microcrystalline cellulose, hydrogenated vegetable oil and sodium laurilsulfate
- capsule shell: gelatin and titanium dioxide (E171)
- printing ink: shellac, black iron oxide (E172) and potassium hydroxide.

Zonisamide 50 mg hard capsules:
The active substance is zonisamide. Each capsule contains 50 mg of zonisamide.

The other ingredients are:
- capsule contents: microcrystalline cellulose, hydrogenated vegetable oil and sodium laurilsulfate
- capsule shell: gelatin and titanium dioxide (E171)
- printing ink: shellac and iron oxide red (E172)

Zonisamide 100 mg hard capsules:
The active substance is zonisamide. Each capsule contains 100 mg of zonisamide.
The other ingredients are:
- capsule contents: microcrystalline cellulose, hydrogenated vegetable oil and sodium laurilsulfate
- capsule shell: gelatin and titanium dioxide (E171)
- printing ink: shellac, black iron oxide (E172) and potassium hydroxide.

What Zonisamide Viatris looks like and contents of the pack

Zonisamide Viatris 25 mg hard capsules have a white body and a white cap, marked ‘Z 25’ in black and contain a white/almost white powder.

Zonisamide Viatris 50 mg hard capsules have a white body and white cap, marked ‘Z 50’ in red and contain a white/almost white powder.

Zonisamide Viatris 100 mg hard capsules have a white body and white cap, marked ‘Z 100’ in black and contain a white/almost white powder.

Zonisamide Viatris 25 mg and 50 mg are available in blister packs of 14, 28, 56 capsules and perforated unit dose blister packs of 14 x 1 capsules.

Zonisamide Viatris 100 mg are available in blister packs of 28, 56, 98 and 196 capsules and perforated unit dose blister packs of 56 x 1 capsules.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Viatris Limited
Damastown Industrial Park,
Mulhuddart, Dublin 15,
DUBLIN
Ireland

Manufacturer
Noucor Health, S.A.
Av Cami Reial 51-57
08184 Palau-Solita i Plegamans – Barcelona
Spain

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Viatris
Tél/Tel: + 32 (0)2 658 61 00

България
Майлан ЕООД
Тел: + 359 2 44 55 400

Lietuva
Viatris UAB
Tel: + 370 5 205 1288

Luxembourg/Luxemburg
Viatris
Tél/Tel: + 32 (0)2 658 61 00

(Belgique/Belgien)

Česká republika
Viatris CZ s.r.o.
Tel: + 420 222 004 400

Danmark
Viatris ApS
Tlf: + 45 28 11 69 32

Deutschland
Viatris Healthcare GmbH
Tel: + 49 800 0700 800

Eesti
Viatris OÜ
Tel: + 372 6363 052

Ελλάδα
Viatris Hellas Ltd
Τηλ: + 30 2100 100 002

España
Viatris Pharmaceuticals S.L.
Tel: + 34 900 102 712

France
Viatris Santé
Tél: + 33 4 37 25 75 00

Hrvatska
Viatris Hrvatska d.o.o.
Tel: + 385 1 23 50 599

Ireland
Viatris Limited
Tel: + 353 1 8711600

Ísland
Icepharma hf.
Sími: + 354 540 8000

Italia
Viatris Italia S.r.l.
Tel: + 39 (0)2 612 46921

Κύπρος
CPO Pharmaceuticals Limited
Τηλ: + 357 22863100

Latvija
Viatris SIA
Tel: + 371 676 055 80

Magyarország
Viatris Healthcare Kft.
Tel.: + 36 1 465 2100

Malta
V.J. Salomone Pharma Ltd
Tel: + 356 21 22 01 74

Nederland
Mylan BV
Tel: + 31 (0)20 426 3300

Norge
Viatris AS
Tlf: + 47 66 75 33 00

Österreich
Viatris Austria GmbH
Tel: + 43 1 86390

Polska
Viatris Healthcare Sp. z o.o.
Tel: + 48 22 546 64 00

Portugal
Mylan, Lda.
Tel: + 351 214 127 200

România
BGP Products SRL
Tel: + 40 372 579 000

Slovenija
Viatris d.o.o.
Tel: + 386 1 23 63 180

Slovenská republika
Viatris Slovakia s.r.o.
Tel: + 421 2 32 199 100

Suomi/Finland
Viatris Oy
Puh/Tel: + 358 20 720 9555

Sverige
Viatris AB
Tel: + 46 (0)8 630 19 00

This leaflet was last revised in MM/YYYY

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu