PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

NAVILIZE 100 mg/ml solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 mg sodium valproate.
Sugar free.
For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection or infusion.
Clear liquid and particles free in a colourless glass ampoule.

4 CLINICAL PARTICULARS

Therapeutic indications

In the treatment of generalised epilepsy, particularly with the following patterns of seizures:

- absence
- myoclonic
- tonic-clonic
- atonic
- mixed

as well as, for partial epilepsy:

- simple or complex seizures
- secondary generalised seizures
- specific syndromes (West, Lennox-Gastaut).

NAVILIZE 100 mg/ml solution for injection or infusion is indicated in patients for whom oral therapy is temporarily not possible.

Posology and method of administration

Posology

Daily dosage requirements vary according to age and body weight.

Adults

Dosage should start at 600 mg/day, where applicable in divided doses, increasing by 200 mg/day at three-day intervals until control is achieved; this is generally within the range of 1 000 to 2 000 mg/day (i.e. 20 – 30 mg/kg body mass). If adequate control has not been achieved after two weeks, the dose may be further increased, in stages, to a maximum of 2 500 mg/day, or one other anti-epileptic medicine may be added at a low dosage. In patients already receiving other therapy, the same pattern should be followed. If increased sedation is observed, dosage of barbiturates or benzodiazepines (e.g. lorazepam) should be reduced as that of NAVILIZE 100 mg/ml is increased; dosage of both NAVILIZE 100 mg/ml and other medicines should be adjusted, during the stabilization period, to give optimum control at the lowest possible combined dosage level, and it may be found possible to maintain optimum control with NAVILIZE 100 mg/ml alone.

Children over 20 kg:

Initial dosage should be 400 mg/day irrespective of mass, where applicable in divided doses, with spaced increases until control is achieved. This is usually within the range of 20 to 30 mg/kg of body mass per day. Where adequate control is not achieved within this range, the dose may be increased to 35 mg/kg body mass per day.

Children under 20 kg:

20 mg/kg of body mass per day; in severe cases, this may be increased but only in patients in whom plasma valproic acid levels can be monitored. Above 40 mg/kg/day, clinical chemistry and haematological parameters should be monitored.

Doses should be adjusted according to individual clinical response. Prophylactic treatment should be established individually with the lowest effective dose.

Patients already satisfactorily treated with NAVILIZE 100 mg/ml may be continued at their current dosage using continuous or repeated infusion. Other patients may be given a slow intravenous injection over 3 - 5 minutes, usually 400 - 800 mg depending on body mass (up to 10 mg/kg) followed by continuous or repeated infusion up to a maximum of 2 500 mg/day.

NAVILIZE 100 mg/ml should be replaced by oral sodium valproate therapy as soon as practicable.

Special populations

Use in the elderly

Although the pharmacokinetics of NAVILIZE 100 mg/ml is modified in the elderly, this is of limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly, and, because of decreased binding to serum albumin, the proportion of free medicine is increased. This will affect the clinical interpretation of plasma valproic acid levels.

In patients with renal insufficiency

It may be necessary to decrease dosage. Dosage should be adjusted according to clinical monitoring since monitoring of plasma concentrations may be misleading (see section 5.2).

Paediatric population

Daily requirement for children is usually in the range of 20 - 30 mg/kg/day and method of administration is as above.

Combined therapy

When starting NAVILIZE 100 mg/ml in patients already on other anticonvulsants, these should be tapered slowly; initiation of NAVILIZE 100 mg/ml therapy should then be gradual, with target dose being reached after about 2 weeks. In certain cases it may be necessary to raise the dose by 5 to 10 mg/kg/day when used in combination with anticonvulsants, which induce liver enzyme activity, e.g. phenytoin, phenobarbitone and carbamazepine. Once known enzyme inducers have been withdrawn, or if side-effects, such as tremor, are experienced, it may be possible to maintain seizure control on a reduced dose of NAVILIZE 100 mg/ml. When barbiturates are being administered concomitantly and particularly if sedation is observed (particularly in children) the dosage of barbiturate should be reduced.

General considerations

The concentration of valproate in plasma that appears to be associated with therapeutic effects is approximately 30 - 100 µg/ml. Optimum dosage is mainly determined by seizure control and routine measurement of plasma levels is unnecessary. However, a method for measurement of plasma levels is available and may be helpful where there is poor control or side-effects are suspected (see section 5.2).

Method of administration

Each ampoule of NAVILIZE 100 mg/ml is for single dose injection only. NAVILIZE 100 mg/ml should be used as soon as practicable after opening and used within 24 hours (see section 6.4). Any unused portion must be discarded.
NAVILIZE 100 mg/ml may be given by direct slow intravenous injection or by infusion using a separate intravenous line in normal saline, dextrose 5 %, or dextrose saline.
NAVILIZE 100 mg/ml should not be administered via the same IV line as other IV additives. The intravenous solution is suitable for infusion in PVC, polythene, or glass containers.

Contraindications

- Hypersensitivity to sodium valproate or to any of the excipients (see section 6.1).
- Pregnancy (see section 4.4).
- NAVILIZE 100 mg/ml should not be used in women of childbearing potential unless other treatments are ineffective or not tolerated (see section 4,4 and 4,6).
- Pre-existing, acute or chronic hepatic dysfunction or family history of severe hepatitis, particularly medicine related.
- Known hepatic porphyria.
- Known urea cycle disorders (see section 4.4).
- Patients known to have mitochondrial disorders caused by mutations in the nuclear gene encoding mitochondrial enzyme polymerase γ (POLG e.g. Alpers-Huttenlocher Syndrome) and in children under two years of age who are suspected of having POLG-related disorder.

NAVILIZE 100 mg/ml should not be injected intramuscularly as it may produce tissue necrosis.

Special warnings and precautions for use

Hepatic dysfunction

Conditions of occurrence

Severe liver damage and/or hepatic failure resulting in fatalities have occurred in patients whose treatment included valproic acid or sodium valproate (as in NAVILIZE 100 mg/ml). Patients most at risk are those on multiple anticonvulsant therapy and children, particularly those under the age of 3 years and those with congenital metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with brain damage and/or mental retardation.
The incidents usually occurred during the first six months of therapy, the period of maximum risk being 2 to 12 weeks, and usually involved multiple anticonvulsant therapy. Monotherapy is to be preferred in this group of patients.
Clinical symptoms are usually more helpful than laboratory investigations in the early stages of hepatic failure. Jaundice, serious or fatal hepatotoxicity may be preceded by nonspecific symptoms, usually of sudden onset, such as loss of seizure control, malaise, asthenia, weakness, lethargy, facial oedema, anorexia, vomiting, abdominal pain, drowsiness, jaundice.
In patients with epilepsy, recurrence of seizures can occur. These are an indication for immediate withdrawal of the medicine. Patients should be monitored closely for the appearance of these symptoms. Patients (and their family and carers) should be instructed to immediately report any such signs to the clinician for investigation should they occur. Investigations including clinical examination and laboratory assessment of liver functions should be undertaken immediately.

Detection

Although published evidence does not establish which, if any investigation could predict this possible adverse effect, liver function tests should be performed (especially in patients at risk) prior to therapy and frequently thereafter until 6 months after the controlling dose is reached, when less frequent monitoring may be appropriate. It is also advisable to monitor tests which reflect protein synthesis, e.g. prothrombin time, serum fibrinogen and albumin levels, especially in those who seem most at risk and those with a prior history of hepatic disease.
A slight increase in liver enzymes may be noted, particularly at the beginning of therapy. They are transient and isolated. More extensive biological investigations (including prothrombin rate) are recommended in those patients. An adjustment of dosage may be considered when appropriate and tests should be repeated as necessary.
Raised liver enzymes are not uncommon during treatment with sodium valproate (as in NAVILIZE 100 mg/ml), particularly if used in conjunction with other anticonvulsants, and are usually transient or respond to dosage reduction. Patients with such biochemical abnormalities should be reassessed clinically and tests of liver function should be monitored more frequently. An abnormally low prothrombin rate, particularly in association with other relevant abnormalities (significant decrease in fibrinogen and coagulation factors; increased bilirubin level and raised transaminases) requires cessation of treatment and the substitution of alternative medicines to avoid precipitating convulsions. Uneventful recovery has been recorded in several cases where therapy with sodium valproate has ceased, but death has occurred in some patients in spite of the medicine being withdrawn. Any concomitant use of salicylates should be stopped since they employ the same metabolic pathway.

Pancreatitis

Cases of life-threatening pancreatitis have been reported in both children and adults receiving sodium valproate (as in NAVILIZE 00 mg/ml). Some cases have occurred shortly after initial use while others have occurred after several years of use. There have also been cases in which pancreatitis recurred after rechallenge with sodium valproate. Some of the cases have been described as haemorrhagic with a rapid progression from initial symptoms to death. Young children are at particular risk, but this risk decreases with increasing age.
Severe seizures, neurological impairment or anticonvulsant therapy may be risk factors. Hepatic failure with pancreatitis increases the risk of fatal outcome.
Patients and guardians should be warned that acute abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical attention. If pancreatitis is diagnosed, NAVILIZE 100 mg/ml should be discontinued and alternative treatment for the underlying medical condition initiated as clinically indicated.

Female children, female adolescents, women of childbearing potential and pregnant women

NAVILIZE 100 mg/ml should not be used in female children, in female adolescents, in women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated because of this high teratogenic potential and risk of developmental disorders in infants exposed *in utero* to valproate. The benefit and risk should be carefully reconsidered at regular treatment reviews, at puberty and urgently when a woman of childbearing potential treated with NAVILIZE 100 mg/ml plans a pregnancy or if she becomes pregnant (see section 4.3).
This assessment is to be made before NAVILIZE 100 mg/ml is prescribed for the first time, or when a woman of childbearing potential treated with NAVILIZE 100 mg/ml plans a pregnancy. Women of childbearing potential must use effective contraception during treatment.
NAVILIZE 100 mg/ml should be initiated and supervised by a specialist experienced in the management of epilepsy or bipolar disorder. Treatment should only be initiated if other treatments are ineffective or not tolerated, and the benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably NAVILIZE 100 mg/ml should be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses during pregnancy.
Women of childbearing potential must use effective contraception during treatment and be informed of the risks associated with the use of sodium valproate (as in NAVILIZE 100 mg/ml) during pregnancy (see section 4.6).
The prescriber must ensure that the patient is provided with comprehensive information on the risks. In particular the prescriber must ensure the patient understands:

- The nature and the magnitude of the risks of exposure during pregnancy, in particular the teratogenic risks and the risks of developmental disorders.
- The need to use effective contraception.
- The need for regular review of treatment.
- The need to rapidly consult her medical practitioner if she is thinking of becoming pregnant or there is a possibility of pregnancy.

In women planning to become pregnant all efforts should be made to switch to an appropriate alternate treatment prior to conception, if possible (see section 4.6).
NAVILIZE 100 mg/ml therapy should only be continued after a reassessment of the benefits and risks of the treatment with NAVILIZE 100 mg/ml for the patient by a medical practitioner experienced in the management of epilepsy or bipolar disorder.

Use in renal impairment

Lower doses may be required since free medicine levels may be high owing to lowered serum albumin and poor urinary excretion of free medicine metabolites. As monitoring of plasma concentrations may be misleading, dosage should be adjusted according to clinical monitoring (see section 5.1).

Lupus erythematosus

Although immune disorders have been noted only exceptionally during the use of sodium valproate, the potential benefit of sodium valproate (as in NAVILIZE 100 mg/ml) should be weighed against its potential risk in patients with systemic lupus erythematosus.

Hyperammonaemia

When urea cycle enzymatic deficiency is suspected, metabolic investigations should be performed prior to treatment because of the risk of hyperammonaemia with NAVILIZE 100 mg/ml.
Hyperammonaemia, which may be present in the absence of abnormal liver function tests, can occur in patients during treatment with sodium valproate (as in NAVILIZE 100 mg/ml). This may occasionally present clinically, with or without lethargy or coma, as vomiting, ataxia and increasing clouding of consciousness. Should these symptoms occur, hyperammonaemic encephalopathy should be considered (see Urea Cycle Disorders) and NAVILIZE 100 mg/ml should be discontinued.

Urea Cycle Disorders (UCD)

Hyperammonaemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy (as in NAVILIZE 100 mg/ml) in patients with urea cycle disorders, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency.
Prior to the initiation of NAVILIZE 100 mg/ml, evaluation for UCD should be considered in the following patients:

1) those with a history of unexplained encephalopathy or coma, encephalopathy associated with a protein load, pregnancy-related or postpartum encephalopathy, unexplained mental retardation, or history of elevated plasma ammonia or glutamine;
2) those with cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low BUN, or protein avoidance;
3) those with a family history of UCD or a family history of unexplained infant deaths (particularly males); (3)
4) those with other signs or symptoms of UCD.

Patients who develop symptoms of unexplained hyperammonaemic encephalopathy while receiving NAVILIZE 100 mg/ml should receive prompt treatment (including discontinuation of NAVILIZE 100 mg/ml therapy) and be evaluated for underlying urea cycle disorders.

Ornithine Transcarbamylase (OTC) Deficiency

The females who are heterozygous for OTC deficiency have a spectrum of clinical and biochemical findings, depending on the extent of inactivation of the X-chromosome. Females may show a range of symptoms due to hyperammonaemia which, may be episodic, and therefore difficult to diagnose. The acute symptoms include headaches, vomiting, irritability, bizarre behaviour, lethargy, ataxia, tremors, seizures (generalised tonic-clonic or focal) and coma.
Valproate (as in NAVILIZE 100 mg/ml) may precipitate hyperammonaemia symptoms in those who have pre-existing OTC deficiency. As the symptoms may include seizures, any female with valproate-associated symptomatic hyperammonaemia should be evaluated for OTC deficiency. Investigations should include measurement of plasma amino acids and the immediate cessation of valproate should result in clinical improvement.
A familial history of infant mortality or patient history of OTC deficiency, or of seizures or coma in the presence of mental retardation suggests the need to exclude OTC deficiency.

Surgery

Prolongation of bleeding time, sometimes with thrombocytopenia, has occurred with sodium valproate (as in NAVILIZE 100 mg/ml) therapy. Platelet function should be monitored before surgery is undertaken in patients receiving NAVILIZE 100 mg/ml.

Other

Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are recommended prior to initiation of therapy or before surgery, and in case of spontaneous bruising or bleeding.

Suicidal behaviour and ideation

Antiepileptic medicines, including sodium valproate (as in NAVILIZE 100 mg/ml) increase the risk of suicidal thoughts or behaviour in patients taking these medicines for any indication. Patients treated with any antiepileptic medicine (AED) for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour, and appropriate treatment should be considered.
The relative risk for suicidal thoughts or behaviour was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.
Anyone considering prescribing sodium valproate or any other AED must balance this risk with the risk of untreated illness.
Should suicidal thoughts and behaviour emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.
Patients, their caregivers, and families should be informed that NAVILIZE 100 mg/ml increases the risk of suicidal thoughts and behaviour and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behaviour, or the emergence of suicidal thoughts, behaviour, or thoughts about self-harm. Behaviours of concern should be reported immediately to the treating doctor.

Abrupt withdrawal

The possible risk of fits after sudden cessation of NAVILIZE 100 mg/ml should be borne in mind. If it is the only anticonvulsant used and has to be withdrawn for more than 12 hours because of surgery, control of epilepsy may be lost.

Carbapenem antibiotics

The concomitant use of sodium valproate (as in NAVILIZE 100 mg/ml) and carbapenem antibiotics is not recommended (see section 4.5).

Patients with known or suspected mitochondrial disease

Valproate (as in NAVILIZE 100 mg/ml) may trigger or worsen clinical signs of underlying mitochondrial diseases caused by mutations of mitochondrial DNA as well as the nuclear-encoded POLG gene. In particular, acute liver failure and liver-related deaths have been associated with valproate treatment at a higher rate in patients with hereditary neurometabolic syndromes caused by mutations in the gene for mitochondrial enzyme polymerase γ (POLG e.g. Alpers-Huttenlocher Syndrome).
POLG-related disorders should be suspected in patients with a family history or suggestive symptoms of a POLG-related disorder, including but not limited to un-explained encephalopathy, refractory epilepsy (focal, myoclonic), status epilepticus at presentation, developmental delays, psychomotor regression, axonal sensorimotor neuropathy, myopathy cerebellar ataxia, opthalmoplegia, or complicated migraine with occipital aura. POLG mutation testing should be performed in accordance with current clinical practice for the diagnostic evaluation of such disorders.

Aggravated convulsion

Some patients may experience, instead of an improvement, a reversible worsening of convulsion frequency and severity (including status epilepticus), or the onset of new types of convulsions with NAVILIZE 100 mg/ml. In case of aggravated convulsions, the patients should be advised to consult their medical practitioner immediately (see section 4.8).

Thrombocytopenia

Because of reports of thrombocytopenia, inhibition of the secondary phase of platelet aggregation, and abnormal coagulation parameters, platelet counts and coagulation tests are recommended before initiating therapy and at periodic intervals. Evidence of haemorrhage, bruising or a disorder of haemostasis/coagulation is an indication for reduction of NAVILIZE 100 mg/ml dosage or withdrawal of therapy.

Weight gain

Patients should be warned of the risk of weight gain at the initiation of therapy, and appropriate strategies should be adopted to minimise the risk (see section 4.8).

Carnitine Palmitoyltransferase (CPT) Type II deficiency

Patients with an underlying carnitine palmitoyltransferase (CPT) type II deficiency should be warned of the greater risk of rhabdomyolysis when using valproate as contained in NAVILIZE 100 mg/ml.

Oestrogen containing medicines

Oestrogen containing medicines, including oestrogen containing hormonal contraceptives, may increase the clearance of NAVILIZE 100 mg/ml, which may result in decreased serum concentration of valproate and potentially decreased valproate efficacy. Prescribers should monitor clinical response (seizure control or mood control) when initiating or discontinuing oestrogen-containing medicines. Consider monitoring of valproate serum levels (see section 4.5).

Use in the elderly

Although the pharmacokinetics of sodium valproate are modified in the elderly, they have limited clinical significance and dosage should be determined by seizure control. The volume of distribution is increased in the elderly and because of decreased binding to serum albumin, the proportion of free medicine is increased. This will affect the clinical interpretation of plasma valproic acid levels.

Paediatric use

The potential benefit of sodium valproate (as in NAVILIZE 100 mg/ml) should be weighed against the risk of pancreatitis or liver damage in such patients prior to initiation of therapy (see section 4.4). The concomitant use of salicylates should be avoided in children under 3 due to the risk of liver toxicity and the concomitant use of barbiturates may require dosage adjustment (see section 4.5). Monotherapy is recommended in children under 3 years of age, when prescribing NAVILIZE 100 mg/ml). Young children are at particular risk for pancreatitis, however this risk decreases with increasing age.

Effects on laboratory tests

Sodium valproate as contained in NAVILIZE 100 mg/ml is eliminated mainly through the kidneys, partly in the form of ketone bodies. This may give false positives in the urine testing of possible diabetics.
There have been reports of altered thyroid function test results associated with sodium valproate. The clinical significance of this is unknown.

Interaction with other medicines and other forms of interaction

Effects of valproate on other medicines

Sodium valproate (as in NAVILIZE 100 mg/ml) is an inhibitor of a variety of hepatic enzymes, including cytochrome P450, glucuronyl transferase and epoxide hydrolase, and may displace various medicines from plasma protein binding sites. The following list provides information about potential effects of valproate co-administration on a range of commonly prescribed medicines. The list is not exhaustive, as new interactions may be reported.
Alcohol: Valproic acid may potentiate the CNS depressant activity of alcohol. Alcohol intake is not recommended during treatment with NAVILIZE 100 mg/ml.
Antiepileptic medicines: Several antiepileptic medicines often used in conjunction with valproate (e.g. phenytoin, carbamazepine, phenobarbital (phenobarbitone) have the ability to increase the intrinsic clearance of valproate, presumably by enzymatic induction of metabolism.
Carbamazepine: Valproate (as in NAVILIZE 100 mg/ml) may displace carbamazepine from protein binding sites and may inhibit the metabolism of both carbamazepine and its metabolite carbamazepine 10, 11 epoxide and consequently potentiate toxic effects of carbamazepine. Clinical monitoring is recommended especially at the beginning of combined therapy, with dosage adjustment when appropriate. Clinical toxicity has been reported when NAVILIZE 100 mg/ml was administered with carbamazepine as valproate may potentiate toxic effect of carbamazepine.
Lamotrigine: Sodium valproate (as in NAVILIZE 100 mg/ml) reduces lamotrigine metabolism and increases its mean half-life. This interaction may lead to increased lamotrigine toxicity, in particular serious skin rashes. Clinical monitoring is recommended, and lamotrigine dosage should be decreased as appropriate.
Phenobarbital (phenobarbitone): Sodium valproate (as in NAVILIZE 100 mg/ml) blocks the metabolism of barbiturates causing an increase in phenobarbital (phenobarbitone) plasma levels, which, particularly in children, may be associated with sedation. Combination of sodium valproate and phenobarbital (phenobarbitone) can cause CNS depression without significant elevation of serum level of either medicine. Therefore, clinical monitoring is recommended throughout the first 15 days of combined treatment. A reduction in the dose of phenobarbital (phenobarbitone) and/or valproate may be necessary and this should also be borne in mind if medicines which are metabolised to phenobarbital (phenobarbitone) (e.g. primidone, methylphenobarbitone) are given with NAVILIZE 100 mg/ml.
Phenytoin: There have been reports of breakthrough seizures occurring with the combination of sodium valproate (as in NAVILIZE 100 mg/ml) and phenytoin.
In addition, a decrease in total serum phenytoin with an increase in the free versus protein bound phenytoin levels has been reported with possible overdose symptoms (valproic acid displaces phenytoin from its plasma protein binding sites and reduces its hepatic catabolism).
Therefore, clinical monitoring is recommended. When phenytoin plasma levels are determined, the free form should be evaluated. The dosage of phenytoin may require adjustment when given in conjunction with NAVILIZE 100 mg/ml as required by the clinical situation.
Ethosuximide: The interaction between ethosuximide and valproate (as in NAVILIZE 100 mg/ml) is not normally of clinical significance. There is evidence that sodium valproate may inhibit ethosuximide metabolism. Patients receiving this combination should be monitored clinically.
Primidone: Valproate increases primidone plasma levels with exacerbation of its adverse effects (such as sedation); these signs cease with long-term treatment. Clinical monitoring is recommended especially at the beginning of combined therapy with dosage adjustment when appropriate.
Medicines with extensive protein binding: The concomitant administration of NAVILIZE 100 mg/ml with medicines that exhibit extensive protein binding (e.g. aspirin, carbamazepine, phenytoin, warfarin) may result in alteration of serum medicine levels.
Anticoagulants: The effect of sodium valproate (as in NAVILIZE 100 mg/ml) on anticoagulants which modify platelet function is unknown (see section 4.8). Caution is recommended when administering anticoagulants and other medicines which have anticoagulant properties (e.g. warfarin and aspirin).
Oral contraceptives: The enzyme inducing effect of valproate (as in NAVILIZE 100 mg/ml) is appreciably less than that of certain other anticonvulsants and loss of efficacy of oral contraceptive medicines does not appear to be a problem.
Psychotropic medicines: Sodium valproate (as in NAVILIZE 100 mg/ml) may potentiate the effects of other psychotropics such as MAOIs, neuroleptics, benzodiazepines and other antidepressants, therefore clinical monitoring is advised and the dose of these medicines should be reduced accordingly.
Clonazepam: The concomitant use of sodium valproate (as contained in NAVILIZE 100 mg/ml) and clonazepam may produce absence status.
Clozapine: Caution is advised during concomitant administration as competitive protein binding may potentiate an increase in clozapine or valproate levels.
Diazepam: Sodium valproate displaces diazepam from its plasma binding sites and inhibits its metabolism. Monitoring of free diazepam levels may be necessary if the patient becomes sedated.
Lorazepam: A decrease in lorazepam plasma clearance may occur with concomitant administration of sodium valproate.
Midazolam: Free plasma midazolam may increase in patients receiving valproate (as contained in NAVILIZE 100 mg/ml). It appears likely that sodium valproate displaces midazolam from its plasma binding sites, potentially leading to an increase of the midazolam response.
Zidovudine: Valproate may raise zidovudine plasma concentrations leading to increased zidovudine toxicity.
Tricyclic antidepressants: Sodium valproate may inhibit the metabolism of tricyclic antidepressants. Clinical monitoring of free antidepressant levels may be necessary.
Olanzapine: Valproic acid may decrease the olanzapine plasma concentration.
Felbamate: Valproic acid may decrease the felbamate mean clearance.
Propofol: Valproic acid may lead to an increased blood level of propofol. When co-administered with valproate, a reduction of the dose of propofol should be considered.
Nimodipine: Concomitant treatment of nimodipine with valproic acid may increase nimodipine plasma concentration.
Other medicines: There was no notable interaction between valproate and lithium.

Effects of other medicines on valproate

The dosage of Sodium valproate may need to be increased by 5 to 10 mg/kg/day when used in combination with medicines which induce hepatic enzymes and thereby increase the clearance of valproate. In contrast, medicines that are inhibitors of cytochrome P450, may be expected to have only a minor effect on valproate clearance as cytochrome P450 mediated microsomal oxidation is a relatively minor secondary metabolic pathway to glucuronidation and ß-oxidation. The list is not exhaustive, as new interactions may be reported.
Valproic acid metabolite levels may be increased in case of concomitant use with phenytoin or phenobarbital (phenobarbitone). Therefore, patients treated with either of these two medicines should be carefully monitored for signs and symptoms of hyperammonaemia.
Aspirin: Concomitant administration of sodium valproate (as contained in NAVILIZE 100 mg/ml) and aspirin may result in displacement of valproate from protein binding sites, resulting in a rise in free levels. In addition, aspirin appears to inhibit the metabolism of valproate. Thus, caution is advisable when patients on NAVILIZE 100 mg/ml are prescribed aspirin. Furthermore, patients requiring long-term aspirin therapy may require a reduction in dosage of sodium valproate.
Felbamate: Felbamate may decrease valproic acid clearance and consequently increase valproate serum concentrations. Valproate dosage should be monitored when given in combination with felbamate.
Phenobarbitone, phenytoin and carbamazepine: These medicines can decrease steady-state valproate levels in patients by increasing the intrinsic clearance of valproate, presumably through enzymic induction of metabolism. The half-life is significantly reduced in patients on polytherapy with these medicines. Dosages should be adjusted according to clinical response and blood levels in case of combined therapy.
Antidepressants: Antidepressants (including MAOIs, tricyclic antidepressants and SSRIs) may have the potential to inhibit the metabolism of valproate via the cytochrome P450 system. However, there is not expected to be any significant interaction within normal therapeutic doses. Antidepressants can lower the seizure threshold of non-stabilised epileptic patients, and so careful and regular monitoring of their condition is indicated.
Clozapine: Caution is advised during concomitant administration as competitive protein binding may potentiate an increase in clozapine or valproate levels.
Chlorpromazine: Chlorpromazine may inhibit the metabolism of valproate.
Fluoxetine: Fluoxetine may inhibit the metabolism of valproate as it does with tricyclic antidepressants, carbamazepine and diazepam.
Mefloquine: Mefloquine increases valproic acid metabolism and has a convulsing effect; therefore, epileptic seizures may occur in cases of combined therapy.
Cimetidine or erythromycin: Valproate serum levels may be increased (as a result of reduced hepatic metabolism) in case of concomitant use with cimetidine or erythromycin.
Carbapenem antibiotics: Decrease in valproate blood level sometimes associated with convulsions has been observed when valproate and carbapenem antibiotics (panipenem, meropenem, imipenem, ertapenem, biapenem) were combined. Due to the rapid onset and the extent of the decrease, co-administration of carbapenem antibiotics in patients stabilised on NAVILIZE 100 mg/ml should be avoided (see section 4.4). If treatment with these antibiotics cannot be avoided, close monitoring of valproate blood level should be performed.
Vitamin K dependent factor anticoagulant: Close monitoring of prothrombin rate should be performed in case of concomitant use of vitamin K dependent factor anticoagulant. Close monitoring of INR should be performed in case of concomitant use of vitamin K dependent factor anticoagulants (e.g. warfarin and other coumarin anticoagulants) because the anticoagulant effect of these medicines may be increased due to displacement from plasma protein binding sites by NAVILIZE 100 mg/ml.
Rifampicin: Rifampicin may decrease the valproate blood levels resulting in a lack of therapeutic effect. Therefore, valproate dosage adjustment may be necessary when it is co-administered with rifampicin.
Protease inhibitors: Protease inhibitors such as lopinavir, ritonavir decrease valproate plasma levels when co-administered
Colestyramine: Colestyramine may lead to a decrease in plasma levels of valproate when co-administered.
Oestrogen containing medicines: Oestrogen containing medicines, including oestrogen containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased serum concentration of valproate and potentially decreased valproate efficacy.
Prescribers should monitor clinical response (seizure control or mood control) when initiating or discontinuing oestrogen-containing medicines. Consider monitoring of valproate serum levels.
The enzyme inducing effect of valproate is appreciably less than that of certain other anticonvulsants and loss of efficacy of oral contraceptive medicines does not appear to be a problem.

Other interactions

Concomitant administration of valproate (as in NAVILIZE 100 mg/ml) and topiramate or acetazolamide has been associated with encephalopathy and/or hyperammonaemia. Patients treated with those two medicines should be carefully monitored for signs and symptoms of hyperammonaemic encephalopathy.
Quetiapine: Co-administration of valproate (as in NAVILIZE 100 mg/ml) and quetiapine may increase the risk of neutropenia/leucopenia.

Fertility, pregnancy and lactation

Pregnancy

The use of NAVILIZE 100 mg/ml in pregnancy and in women of childbearing potential is contraindicated, unless there is no suitable alternative treatment of epilepsy (see section 4.3).

Risk associated with sodium valproate

In animals, teratogenic effects have been demonstrated in mice, rats and rabbits.

Congenital malformations

The risk of a mother with epilepsy giving birth to a baby with an abnormality is about three times that of the normal population. An increased incidence of malformations including neural tube defects, craniofacial defects, malformation of the limbs, cardiovascular malformations, hypospadias and multiple anomalies involving various body systems has been reported in children born to mothers treated with valproate (as in NAVILIZE 100 mg/ml), when compared to the incidence for certain other antiepileptic medicines.
Data has shown an incidence of congenital malformations in children born to epileptic women exposed to valproate (as in NAVILIZE 100 mg/ml) monotherapy during pregnancy. This is a greater risk of major malformations than for the general population. Women treated with NAVILIZE 100 mg/ml have a potentially increased risk of giving birth to a baby with an abnormality due to the higher C_{max} of the intravenous formulation compared with the oral formulation.
Mothers taking more than one anticonvulsant medicine might have a higher risk of having a baby with a malformation than mothers taking one medicine.
NAVILIZE 100 mg/ml, if administered in the first trimester of pregnancy, is suspected of causing an increased risk of neural tube defects (especially spina bifida) in the exposed foetus. This has been estimated to be in the region of 1 - 2 %. This risk is dose dependent but a threshold dose below which no risk exists cannot be established.

Developmental disorders

Data has shown that exposure to valproate *in utero* can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.
Studies in pre-school children exposed *in utero* to valproate show that some children may experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.
Some data have suggested an association between *in utero* valproate exposure and the risk of developmental delay (frequently associated with craniofacial abnormalities), particularly of verbal IQ. IQ measured in school aged children with a history of valproate exposure in utero, was lower than those children exposed to other antiepileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate (as in NAVILIZE 100 mg/ml) that the risk of intellectual impairment may be independent from maternal IQ. There is limited data on the long-term outcomes.
Developmental delay has been very rarely reported in children born to mothers with epilepsy. It is not possible to differentiate what may be due to genetic, social, environmental factors, maternal epilepsy or antiepileptic treatment.
Autism spectrum disorders have also been reported in children exposed to valproate *in utero*.
Data suggests that children exposed to valproate *in utero* may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).

Valproate therapy in pregnancy

If a woman treated with valproate (as in NAVILIZE 100 mg/ml) plans a pregnancy or becomes pregnant, the valproate should be stopped and be replaced with medicines that are less harmful in pregnancy.
Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcome. Available data suggest that antiepileptic polytherapy including valproate (as in NAVILIZE 100 mg/ml) is associated with a higher risk of abnormal pregnancy outcome than valproate monotherapy.
In view of this data, the following recommendation should be taken into consideration:
NAVILIZE 100 mg/ml should not be used during pregnancy and in women of child-bearing potential unless clearly necessary (see section 4.3), that is, in situations where other treatments are ineffective or not tolerated. This assessment is to be made before NAVILIZE 100 mg/ml is prescribed for the first time, or when a woman of childbearing potential treated with NAVILIZE 100 mg/ml plans a pregnancy. Women of childbearing potential must use effective contraception during treatment.
The enzyme inducing effect of valproate is appreciably less than that of certain other anticonvulsants and loss of efficacy of oral contraceptive medicines does not appear to be a problem.

However, oestrogen containing medicines, including oestrogen containing hormonal contraceptives, may increase the clearance of valproate, which may result in decreased serum concentration of valproate and potentially decreased valproate efficacy. Prescribers should monitor clinical response (seizure control or mood control) when initiating or discontinuing oestrogen-containing medicines. Consider monitoring of valproate serum levels.
Women of childbearing potential should be informed of the risks (foetal birth defects and adverse cognitive effects) and benefits of the use of valproate during pregnancy.
Women receiving NAVILIZE 100 mg/ml who become or wish to become pregnant should be encouraged to consider routine ultrasound and amniocenteses for prenatal diagnosis of such abnormalities. As folic acid may have a role in the prevention of neural tube defects in infants of women taking antiepileptic therapy, such women are recommended to take folic acid supplementation (5 mg daily) four weeks prior to and 12 weeks after conception.
Notwithstanding the potential risks, no sudden discontinuation of antiepileptic therapy should be undertaken, without reassessment of the risks and benefits, as this may lead to breakthrough seizures which could have serious consequences for both the mother and the foetus. If after careful evaluation of the risks and benefits, sodium valproate treatment is to be continued during pregnancy, it is recommended to:

- Use the effective dose and divide the daily dose of NAVILIZE 100 mg/ml into several small doses to be taken throughout the day. The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations
- All patients with a NAVILIZE 100 mg/ml exposed pregnancy and their partners should be referred to a medical practitioner *experienced in teratology/pre-natal medicine* for evaluation and counselling regarding the exposed pregnancy. Specialised prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations
- If appropriate, folate supplementation should be started before pregnancy and at relevant dosage (5 mg daily) as it may reduce the risk of neural tube defects. However, available evidence does not suggest this prevents the birth defects or malformations due to NAVILIZE 100 mg/ml exposure.

Before NAVILIZE 100 mg/ml is prescribed for use in women with epilepsy of any form, who could become pregnant, they should receive specialist advice. Due to the potential risks to the foetus, the benefits of its use should be weighed against the risks. When treatment with NAVILIZE 100 mg/ml is deemed necessary, precautions to minimise the potential teratogenic risk should be followed (see above recommendations).

Risk in the neonate

There have been less frequent reports of haemorrhagic syndrome in neonates whose mothers have received sodium valproate (as in NAVILIZE 100 mg/ml) during pregnancy. This syndrome is related to thrombocytopenia, hypofibrinaemia, and/or to a decrease in other coagulation factors. Afibrinaemia has also been reported and may be fatal. Hypofibrinaemia is possibly associated with a decrease of coagulation factors. Haemorrhagic syndrome must be distinguished from the decreased of the vitamin-K factors induced by phenobarbital (phenobarbitone) and other enzyme inducers. Platelet count, fibrinogen plasma level and coagulation status should be investigated in neonates.
Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproate (as in NAVILIZE 100 mg/ml) during the third trimester of the pregnancy.
Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate (as in NAVILIZE 100 mg/ml) during pregnancy.
Withdrawal syndrome (such as, in particular, agitation, irritability, hyperexcitability, jitterness, hyperkinesia, tonicity disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have received valproate (as in NAVILIZE 100 mg/ml) during the last trimester of pregnancy.

Breastfeeding

Sodium valproate is excreted in breast milk. Concentrations in breast milk have been reported to be 1 to 10 % of serum concentration. It is not known what effect this would have on a breastfed infant. Mothers taking NAVILIZE 100 mg/ml should not breastfeed their babies.

Fertility

Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (as in NAVILIZE 100 mg/ml). NAVILIZE 100 mg/ml administration may also impair fertility in men (see section 4.8).

Effects on ability to drive and use machines

Use of NAVILIZE 100 mg/ml may provide seizure control such that the patient may be eligible to hold a driving licence. However, patients should be warned of the risk of drowsiness, especially in cases of anticonvulsant polytherapy, too high a starting dose, too rapid a dose escalation or when used in association with benzodiazepines.

Undesirable effects

a. Summary of the safety profile

The adverse events expected for the intravenous formulation of sodium valproate are identical to those expected for the oral formulations currently available with the exception of local administration site reactions.
Congenital malformations and developmental disorders: (see sections 4.4 and 4.6).

b. Tabulated summary of adverse reactions

The adverse reactions are listed below according to system organ class and frequencies indicated as frequent, less frequent and frequency unknown.

System organ class	Frequency	Adverse reactions
Neoplasms benign, malignant and unspecified	Less frequent	Myelodysplastic syndrome
Blood and lymphatic system disorders	Frequent	Thrombocytopenia, anaemia
	Less frequent	Leukopenia, pancytopenia, reduction of fibrinogen, prolonged prothrombin time, bone marrow failure, including pure red cell aplasia, agranulocytosis, anaemia macrocytic and macrocytosis, spontaneous bruising or bleeding (see section 4.4), red cell hypoplasia, neutropenia
Immune system disorders	Frequency unknown	Angioedema, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome, allergic reactions
Endocrine disorders	Less frequent	Hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or androgen increased), Syndrome of Inappropriate Secretion of ADH (SIADH), hypothyroidism
Metabolism and nutrition disorders	Frequent	Hyponatremia, asymptomatic elevations of ammonia, increased weight (see section 4.4)
	Less frequent	Obesity (3), hyperammonemia, hyperammonemia associated with neurological symptoms (see section 4.4)
Psychiatric disorders	Frequent	Confusional state, hallucinations, aggression, agitation, disturbance in attention, abnormal behaviour, psychomotor hyperactivity and learning disorder
Nervous system disorders	Frequent	Tremor, stupor, somnolence, convulsion , memory impairment, headache, nystagmus, dizziness, extrapyramidal disorder which may not be reversible, including reversible parkinsonism
	Less frequent	Ataxia, coma, encephalopathy, aggravated convulsions (see section 4.4), lethargy, paraesthesia, reversible parkinsonism, diplopia, depression, excitement, hyperactivity and behavioural disorders, dementia associated with reversible cerebral atrophy and cognitive disorder
Ear and labyrinth disorders	Frequent	Deafness, either reversible or irreversible
Vascular disorders	Frequent	Haemorrhage
	Less frequent	Vasculitis
Respiratory, thoracic and mediastinal disorders	Less frequent	Pleural effusion
Gastrointestinal disorders	Frequent	Nausea, vomiting, upper abdominal pain, diarrhoea, disorder (mainly gingival hyperplasia), stomatitis, anorexia, increased appetite
	Less frequent	Pancreatitis, sometimes lethal (see section 4.4)
Hepato-biliary disorders	Frequent	Liver injury
	Less frequent	Hepatic dysfunction, including hepatic failure resulting in fatalities (see section 4.4)
Skin and subcutaneous tissue disorders	Frequent	Hypersensitivity, transient and (or) dose related alopecia, nail and nail bed disorders
	Less frequent	Hirsutism, acne and male pattern alopecia (see Endocrine disorders), angioedema, rash and hair disorder (such as hair texture abnormal, hair colour changes, hair growth abnormal)
	Frequency unknown	Cutaneous reactions such as exanthematous rash, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme
Musculoskeletal and connective tissue disorders	Less frequent	Decreased bone mineral density, osteopenia, osteoporosis and fractures, systemic lupus erythematosus, rhabdomyolysis
Renal and urinary disorders	Frequent	Urinary incontinence
	Less frequent	Renal failure, enuresis, tubulointerstitial nephritis, reversible Fanconi's syndrome
Reproductive system and breast disorders	Frequent	Dysmenorrhoea
	Frequency unknown	Amenorrhoea, irregular periods, male infertility, polycystic ovaries, breast enlargement, galactorrhoea
Congenital, familial and genetic disorders	Frequency unknown	Congenital malformations, developmental disorders (see section 4.6)
General disorders and administration site conditions	Less frequent	Non-severe peripheral oedema, hypothermia, oedema, increase in appetite
Investigations	Less frequent	Decreased coagulation factors, abnormal coagulation tests (such as prolonged prothrombin time, activated partial thromboplastin time, thrombin time and INR), biotin deficiency/biotinidase deficiency

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

Overdose

Symptoms

Clinical signs of acute massive overdose usually include a coma, with muscular hypotonia, hyporeflexia, miosis and impaired respiratory function.
Symptoms may however be variable and seizures have been reported in the presence of very high plasma levels. Cases of intracranial hypertension related to cerebral oedema have been reported.

Treatment

Hospital management of overdose should be symptomatic: cardio-respiratory monitoring, assisted ventilation and other supportive measures are recommended. Haemodialysis and haemoperfusion have been used successfully.
Naloxone has been successfully used in a few isolated cases.
Deaths have occurred following massive overdose.

5 PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, ATC Code: N03AG01
Pharmacological classification: A 2.5 Anticonvulsants, including anti-epileptics.

Sodium valproate has anticonvulsant properties. The exact mode of action is unknown. However, the most likely mode of action for valproate is potentiation of the inhibitory action of gamma amino butyric acid (GABA) through an action on the further synthesis or further metabolism of GABA.

Pharmacokinetic properties

Absorption

The pharmacokinetic profile of sodium valproate IV injection differs from that of oral sodium valproate preparations. As expected, after intravenous and oral dosage (enteric coated tablets) of sodium valproate (400 mg), T_{max} is reached sooner following intravenous administration (7,3 ± 2,6 min) than after oral administration (227,7 ± 59,2 min) and C_{max} is higher after intravenous dosage (55,4 ± 9,38 microgram/ml) than after oral administration (39,1 ± 3,51 microgram/ml). The bioavailability of sodium valproate enteric-coated (EC) tablets is only slightly less than that of intravenous sodium valproate with a mean AUC ratio of 100:87 for intravenous to oral forms respectively. The distribution, metabolism, excretion and elimination of intravenous sodium valproate are not different to orally administered sodium valproate.
In most adult patients, daily doses of 1,200 to 1,500 mg result in therapeutic plasma levels of 50 to 100 microgram/ml (0,35 to 0,69 mmol/l). However, correlation between the daily dose per bodyweight and plasma levels of medicine has been poor.

Distribution

Distribution of sodium valproate is rapid and most likely restricted to the circulation and rapidly exchangeable extracellular water. CSF and breast milk levels were found to be 5 to 15 % and about 1 to 10 % of plasma levels, respectively.
Sodium valproate is approximately 90 % bound to plasma proteins but only 60 % to albumin.
However, if the plasma level of valproic acid rises above 120 microgram/ml or if the serum albumin concentration is lowered, the binding sites may become saturated, causing the amount of free medicine to rise rapidly, out of proportion to any increase in dosage. Sodium valproate may displace phenobarbital (phenobarbitone) or phenytoin from plasma protein binding sites.
Saliva levels of sodium valproate are poorly correlated with those in plasma in contrast to the good correlation found for other antiepileptics.
In animals, the medicine crosses the placenta.

Biotransformation

Its metabolism is complex; the major elimination pathway is via glucuronidation (40 – 60 %). The remainder is largely metabolised via oxidation pathways, β-oxidation accounting for 30 – 40 % and w-oxidation (cytochrome P450 dependent), the remaining fraction. Only 1 to 3 % of the ingested dose is found to be excreted unchanged in the urine.

Elimination

Sodium valproate is almost completely metabolised prior to excretion. Plasma half-life is variable but generally appears to be 8 to 12 hours (range 3,84 to 15,77 hours). It may be shorter in patients receiving other anticonvulsants or in children and patients receiving the medicine for long periods. In cases of overdose, long half-lives up to 30 hours have been reported. Antipsychotic medicines or antidepressants including MAOIs, tricyclics and SSRIs co-administered with sodium valproate may result in competitive metabolism or enzyme inhibition, thereby increasing valproate levels (see section 4.5).

Linearity/non-linearity

Valproic acid shows non-linear kinetics, due to concentration-dependent plasma protein binding as well as a relatively short half-life.

6 PHARMACEUTICAL PARTICULARS

List of excipients

Disodium phosphate dodecahydrate
Potassium dihydrogen phosphate
Water for injections

Incompatibilities

NAVILIZE 100 mg/ml should not be administered via the same IV line as other IV additives. The intravenous solution is suitable for infusion in PVC, polythene, or glass containers (see section 4.2).

Shelf life

48 months.

Special precautions for storage

Store at or below 30 °C.
To reduce microbiological hazard, use as soon as practicable after opening. If storage is necessary, hold at 2 to 8 ºC for not more than 24 hours.

Nature and contents of container

NACACON 100 mg/ml solution for injection or infusion is packed in type I transparent glass ampoules of 5 ml and 10 ml.

- 3 ml of solution packed in 5 ml capacity glass ampoule.
- 4 ml of solution packed in 5 ml capacity glass ampoule.
- 10 ml of solution packed in 10 ml capacity glass ampoule.

Pack sizes: 1, 4 or 5 ampoules placed in a white plastic tray per outer cardboard box. Not all pack sizes may be marketed.

Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Kahma Biotech (Pty) Ltd
106, 16th Road
Midrand

8 REGISTRATION NUMBERS

NAVILIZE 100 mg/ml (3 ml): 55/2.5/ 0551
NAVILIZE 100 mg/ml (4 ml): 55/2.5/ 0552
NAVILIZE 100 mg/ml (10 ml): 55/2.5/ 0553

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02 May 2023

10 DATE OF REVISION OF THE TEXT

NA