SUMMARY OF PRODUCT CHARACTERISTICS

Assival® Teva 10mg/2ml
Solution for IM or IV Injection

1. NAME OF THE MEDICINAL PRODUCT

Assival® Teva 10mg/2ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule of 2 ml solution for injection contains 10 mg Diazepam.

Excipients with known effect:
benzyl alcohol (30 mg/2 ml), benzoic acid (1mg/ml), sodium benzoate (49mg/ml), propylene glycol (400mg/ml) and ethanol (13.12 % by volume).
For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colorless to slightly green-yellowish solution.

4. CLINICAL PARTICULARS

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS

- Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death *[*see sections *4.4 and 4.5]*.
- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.

Follow patients for signs and symptoms of respiratory depression and sedation**.**

4.1 Therapeutic indications

Symptomatic relief of tension and anxiety either alone or when associated with stressful situations.
Psychoneurotic states manifested by tension, anxiety, apprehension, fatigue and depressive symptoms.

In acute alcohol withdrawal, Assival Teva may be useful in the symptomatic relief of tremor, impending or acute delirium tremens and hallucinosis.
Assival Teva is a useful adjunct in the relief of skeletal muscle spasms, spasticity, stiff-man syndrome and tetanus.
When used intravenously, Assival Teva Injection is a useful adjunct in status epilepticus and severe recurrent convulsive seizures.
As premedication in patients undergoing surgical procedures (the intra-muscular route is preferred) or in patients undergoing cardioversion (when the intravenous route is preferred).

4.2 Posology and method of administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

For intravenous administration, the drug shoud be injected slowly, maximum 5 mg (1 ml) per minute; small veins (e.g. dorsum of hand or wrist) should not be used. Extreme care should be taken to avoid intra-arterial administration or extravasation.
If it is not feasible to administer Assival Teva directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.
When Assival Teva is administered intramuscularly, it should be injected deeply into the muscle.
Once the acute symptomatology has been controlled with injectable Assival Teva, the patient may be placed on oral therapy with Assival if further treatment is required.

Dosage should be individualized for maximum beneficial effect.
The usual recommended dose in older children and adults ranges from 2-20 mg I.M. or I.V. depending on the indication and its severity. In some conditions, larger doses may be required. In such cases doses should be increased cautiously to avoid adverse effects.

In acute conditions, the injection may be repeated within 1 hour although an interval of 3-4 hours is usually satisfactory.
Lower doses (usually 2-5 mg) with a slow increase in dosage, should be used for elderly or debilitated patients and when other sedative drugs are administered simultaneously.

Recommended doses as per specific indications are listed below:

Adults
Moderate Anxiety Disorders and Symptoms of Anxiety
2-5 mg I.M. or I.V. Repeat after 3- 4 hours, if necessary.

Severe Anxiety Disorders and Symptoms of Anxiety
5-10 mg, I.M. or I.V. Repeat after 3 to 4 hours, if necessary.

Acute Alcohol Withdrawal
Initially, 10 mg I.M. or I.V., then 5-10 mg after 3 to 4 hours, if necessary.

Endoscopic Procedures
The I.V. dosage should be titrated to the desired sedative response, such as slurring of speech, with slow administration immediately prior to the procedure. Generally 10 mg or

less is adequate, but up to 20 mg I.V. may be given, particularly when concomitant narcotics are omitted. If I.V. administration cannot be used, 5-10 mg should be given I.M. approximately 30 minutes prior to the procedure.

Muscle Spasm
5-10 mg I.M. or I.V. initially, then 5-10 mg after 3-4 hours, if necessary. For tetanus, larger doses may be required.

Status Epilepticus and Severe Recurrent Convulsive Seizures
Initially 5-10 mg (I.V. preferred). If necessary, this injection may be repeated at 10-15 minute intervals up to a maximum dose of 30 mg.
Extreme caution must be exercised with individuals with chronic lung disease or unstable cardiovascular status.

Preoperative Medication
10 mg I.M. (preferred route), before surgery.

Cardioversion
5-15 mg, I.V., within 5-10 minutes prior to the procedure.

Children
Note: Since Assival Teva Solution for Injection contains benzyl alcohol, this preparation should not be administered to neonates and premature infants.

To obtain maximum clinical effect with minimum amount of drug, and to reduce the risk of hazardous side effects such as apnea or prolonged periods of somnolence, the drug should be administered slowly over 3 minutes, not exceeding 0.25 mg/kg. After an interval of 15-30 minutes, the initial dose can be repeated. If relief of symptoms is not obtained after a third dose, appropriate adjunctive therapy is recommended. Facilities for respiratory assistance should be readily available.

Muscle Spasm
For tetanus in infants over 30 days of age, 1-2 mg I.M. or I.V., slowly, repeated every 3-4 hours, as necessary. In children 5 years or older, 5-10 mg, repeated every 3 to 4 hours, may be required to control tetanus spasms. Respiratory assistance should be available.

Status Epilepticus and Severe Recurrent Convulsive Seizures
Infants over 30 days of age and children under 5 years, 0.2-0.5 mg, slowly, every 2-5 minutes, up to a maximum of 5 mg (I.V. preferred). Children 5 years or older,
1 mg every 2-5 minutes, up to a maximum of 10 mg (slow I.V. administration preferred). Repeat after 2-4 hours if necessary.
EEG monitoring of the seizure may be helpful.

Special populations
Elderly or debilitated patients as well as patients with organic brain changes, circulatory or respiratory insufficiency or with impaired hepatic or renal function shall receive lower doses.
Dose increase, if necessary, should take place gradually and should be guided by the effect achieved.

This also applies for patients that take concomitantly other drugs acting on the central nervous system.

4.3 Contraindications

Assival Teva 10 mg/2 ml solution for injection must **NOT** be used in:

- Hypersensitivity to diazepam, other benzodiazepines or any of the excipients mentioned in Section 6.1
- First trimester of pregnancy and in breastfeeding
- History of dependency (alcohol, medicines, drugs)
- Acute intoxication with alcohol, sleeping pills, analgesics (opiates) as well as psychotropic drugs (neuroleptics, antidepressants, lithium)
- Myasthenia gravis
- Spinal and cerebral ataxia
- Severe respiratory failure
- Sleep apnea syndrome
- Severe hepatic failure
- Premature or newborn babies up to the age of 1 month because of the benzyl alcohol content

4.4 Special warnings and precautions for use

Risks due to simultaneous use with opioids:
The simultaneous use of *Assival Teva 10 mg/2 ml solution for injection* and opioids can cause sedation, respiratory depression, coma and death. Due to these risks, sedatives such as benzodiazepine or related drugs such as *Assival Teva 10 mg/2 ml solution for injection* should only be prescribed together with opioids in patients for whom there are no alternative treatment options. If, however, a simultaneous prescription for *Assival Teva 10 mg/2 ml solution for injection* together with opioids is deemed necessary, then the lowest effective dose should be used and the treatment duration should be as short as possible (see also the general dosage recommendation in section 4.2).
Patients should be closely monitored for signs and symptoms of respiratory depression and sedation. In this regard it is strongly recommended that patients and their caregivers (where applicable) be informed about these symptoms (see section 4.5).

At the beginning of therapy, patient's individual response to the drug should be monitored, in order to identify as soon as possible any relative overdose due to accumulation. This applies in particular to elderly and debilitated patients, children and adolescents, as well as patients with organic brain changes, circulatory or respiratory failure or with impaired hepatic or renal function. Furthermore, patients should be instructed about conduct in relation to everyday activities, while taking into account their specific situation (e.g. professional activity).

After ambulatory administration for diagnostic purposes, the patient should be discharged home only after 1 hour and only if accompanied by another person. Moreover, the patient should be advised not to consume alcohol.

Diazepam should not be taken concomitantly with alcohol and/or drugs with a depressant action on the central nervous system. Concomitant use can enhance the effects of diazepam and possibly lead to deep sedation and clinically relevant cardiovascular and/or respiratory depression (see Section 4.5).

In elderly patients, caution is required because of the risk of falls, particularly when getting up at night.

High-risk patients
Benzodiazepines are not recommended for the primary treatment of psychoses.

Benzodiazepines should not be used as the sole means of treatment of depressions or anxiety states accompanied by depression. In some circumstances, the depressive symptoms can be exacerbated in the absence of appropriate treatment of the underlying disease with antidepressants (danger of suicide).

In epileptic patients, the sudden discontinuation of diazepam can cause seizures.

In elderly and debilitated patients, as well as in patients with heart failure and/or hypotension, whose response to benzodiazepines is often stronger than desired, and in patients with organic brain changes, the prescription should be carefully considered. This also applies to patients with impaired renal function. If necessary, the dose should be reduced or diazepam should be discontinued (see Section 4.2).

A lower dose is also recommended for patients with chronic respiratory failure because of the risk of respiratory depression (see Section 4.2).

Although a fall in blood pressure does not occur often, diazepam should be used with caution in patients in whom a fall in blood pressure could cause cardiac complications. This applies in particular to elderly patients.

Patients with severe hepatic impairment must not be treated with benzodiazepines, because of the risk of encephalopathy (see Section 4.3).

Patients with dependency on medicines with a depressant action on the central nervous system, including alcohol, should not be treated with diazepam, except in cases of acute withdrawal reactions.

Patients with hypovolemic shock may be treated with the injection form only if measures to compensate for the volume deficiency are taken simultaneously.

Patients in a coma may be treated with the injection form only in case of severe restlessness or convulsive states provided the coma has not been caused by intoxication.

In patients with allergic skin disease, increased vascular permeability, or hematopoietic disorders, the solution for injection should be administered with particular care.

Development of tolerance
After repeated use of benzodiazepines over a few weeks, a loss of effectiveness (tolerance) is possible.

In pre-existing alcohol or barbiturate dependency, cross tolerance is possible.

Development of dependency
The use of benzodiazepines can lead to the development of psychological and physical dependency. This is true not only for inappropriate use of particularly high doses, but also for the therapeutic dosage range. The risk of dependency increases with the dose and with the duration of the treatment. This risk is also increased in patients with a history of alcohol, medicine or drugs dependency.

Uninterrupted use for a period longer than 4 weeks should be avoided, as it can lead to dependency.

If physical dependency has developed, withdrawal symptoms occur in case of sudden discontinuation (see below).

Discontinuation withdrawal symptoms
Withdrawal symptoms are possible especially when discontinuing longer-term treatment. These symptoms are manifested as sleeping disorders, increased dreaming, headaches, muscular pain, anxiety, states of tension, inner restlessness, sweating, shaking, mood changes, confusion and irritability.

In severe cases, the following symptoms can also appear:
states of confusion, depersonalization, derealization, hypersensitivity to light, noise and body contact, numbness and paraesthesia in the extremities, epileptic seizures, hallucinations and symptomatic psychoses (e.g. withdrawal delirium).

The sudden discontinuation of a shorter treatment can also cause transient withdrawal signs (rebound phenomena), in which the symptoms that had led to the treatment with diazepam reappear in a more severe form. Accompanying reactions such as mood changes, states of anxiety and restlessness are possible.

As the risk of withdrawal or discontinuation phenomena is higher after sudden treatment discontinuation, it is recommended that the therapy be discontinues by gradual reduction of the dose.

It is recommended that at the beginning of the therapy the patient be advised on the limited treatment period and be explained in detail about the gradual reduction of the dose. Moreover, it is important that the patient be aware of the possibility of rebound phenomena, as a result of which the fear of such symptoms – should they appear upon discontinuation of the drug – can be minimized.

Amnesia
Benzodiazepines can cause anterograde amnesias. This means that (in most cases a few hours) after use of the medicinal product the patient may carry out actions which will not be remembered by him subsequently.

This risk increases with the dose and can be diminished by a sufficiently long uninterrupted period of sleep (7-8 hours).

Mental and "paradoxical" reactions

The use of benzodiazepines can cause, especially in elderly patients or in children, mental as well as so-called "paradoxical" reactions (see Section 4.8). In such cases, the treatment with this preparation should be stopped.

Children and adolescents
Treatment of children or adolescents with *Assival Teva 10 mg/2 ml solution for injection* should take place only if there is an urgent indication (see Section 4.2).

The safety and the effectiveness of diazepam in children of less than 6 months of age were not studied. In this age group, *Assival Teva 10 mg/2 ml solution for injection* should be used with outmost care and only if no other therapeutic alternatives are available.

In the newborn and especially in premature babies, the benzyl alcohol contained in *Assival Teva 10 mg/2 ml solution for injection* can lead to irreversible damage. For this reason, *Assival Teva 10 mg/2 ml solution for injection* must not be used in newborn and in premature babies (see Section 4.3).

Excipients

- This medicine contains 15 mg benzyl alcohol per ml.
  Benzyl alcohol has been linked to serious side effects (“gasping syndrome”) in neonates and small children.
  In small children (under the age of 3 years), the medicine is not to be used for longer than 1 week due to accumulation.
  Due to the risk of accumulation and toxicity (metabolic acidosis), large quantities of benzyl alcohol should be used with caution and only when absolutely necessary, particularly in patients with impaired hepatic or renal function or during pregnancy and breast-feeding (see Contraindications 4.3)

- This drug contains 1 mg benzoic acid and 49 mg sodium benzoate per ml of solution for injection.

- This drug contains less than 1 mmol sodium (23 mg) per ml of solution for injection, that is to say essentially “sodium-free”.

- This drug contains 400 mg propylene glycol per ml of solution for injection.
  Simultaneous use with an alcohol dehydrogenase substrate, such as ethanol, can cause serious side effects in children under the age of 5 years.
  Reproductive or developmental toxicity have not been demonstrated for propylene glycol; however, it can reach the fetus and has been detected in breast milk. The use of propylene glycol in pregnant and breast-feeding patients should be assessed on a case-by-case basis (see Contraindications 4.3).
  Medical monitoring is required in patients with impaired renal or hepatic function, as various undesirable effects have been reported that are associated with propylene glycol, e.g. renal dysfunction (acute tubular necrosis), acute kidney injury and hepatic dysfunction.

- This drug contains 13.12% alcohol by volume.
  Because of the alcohol content, the use *of Assival Teva 10 mg/2 ml solution for injection* can lead to positive results in doping tests.

4.5 Interactions with other medicinal products and other forms of interaction

Opioids
The simultaneous use of sedatives such as benzodiazepines or other related medicinal products such as *Assival Teva 10 mg/2 ml solution for injection* with opioids increases the risk of sedation, respiratory depression, coma and death due to an additive depressive effect on the CNS. The dosage and duration of any simultaneous use should be limited (see section 4.4).

The oxidative breakdown of diazepam into N-desmethyldiazepam, 3-hydroxydiazepam (temazepam) and oxazepam is catalyzed by Cytochrome-P450-isoenzymes CYP2C19 and CYP3A. In vitro studies have shown that hydroxylation is mainly mediated by CYP3A, whereas both isoenzymes CYP3A and CYP2C19 are involved in the N-demethylation. These in vitro observations were confirmed by findings from in vivo studies with subjects.

Concomitantly used medicinal products, containing active substances that are also substrates of CYP3A and/or CYP2C19 can therefore alter the pharmacokinetics of diazepam. Thus, known CYP3A or CYP2C19 inhibitors such as cimetidine, omeprazole, disulfiram, ketoconazole, fluvoxamine and fluoxetine can lead to deep and prolonged sedation.

In case of concomitant use of diazepam with the following medicinal products, mutual enhancement of the sedative, respiratory and hemodynamic effects is possible:
- Sedatives, hypnotics, narcotic analgesics, anesthetics
- Neuroleptics
- Antiepileptics
- Anxiolytics
- Sedating antihistamines
- Antidepressants, lithium preparations
- 4-hydroxybutanoic acid (sodium oxybate)
- HIV protease inhibitors

This applies, in particular, to simultaneous alcohol consumption, which can change and enhance the effects of diazepam in an unpredictable manner.

Moreover, combination with narcotic analgesics can cause an intensification of the euphoric effect and thus to accelerated development of dependency.

In case of simultaneous administration of muscle relaxants, the relaxant effect is enhanced, especially in elderly patients and with higher doses (risk of falls).

In smokers, the elimination of diazepam can be accelerated.

Theophylline in low doses removes the sedation caused by diazepam.

Diazepam can inhibit the action of levodopa.

In rare cases, diazepam can inhibit the metabolism of phenytoin and enhance its effect. phenobarbital and phenytoin can accelerate the metabolism of diazepam.

Because of the slow elimination of diazepam, possible interactions are to be expected even after discontinuation of diazepam treatment.

In patients on long-term therapy with other medicinal products, such as centrally acting antihypertensives, β-blockers, anticoagulants and cardiac glycosides, the nature and extent of the interactions are not reliably predictable. The treating physician should verify the existence of long-term treatments prior to the administration of diazepam. Therefore, particular caution is required if the preparation is used concomitantly, especially at the beginning of the treatment.

4.6 Fertility, pregnancy and lactation

Women of childbearing age
If diazepam is used in a female patient of childbearing age, she should be advised to contact her physician immediately if she wishes to become pregnant or if she suspects pregnancy.

Pregnancy
In pregnancy, diazepam should be used only in exceptional cases with stringent indication – neither in high doses nor over a prolonged period.

Diazepam and its main metabolite N-desmethyldiazepam cross the placenta. Diazepam accumulates in the fetal compartment and the blood of the newborn can reach concentrations that are three times those of the maternal concentration.

The malformation risk in humans after use of therapeutic doses of benzodiazepines in early pregnancy seems to be low, although a number of epidemiological studies have provided evidence of an increased risl of cleft palate.

There are case reports of malformations and intellectual disability in prenatally exposed children after benzodiazepine overdoses and intoxication.

Children of mothers who, during the pregnancy, have received benzodiazepines over a longer period can develop physical dependency. These children present withdrawal symptoms in the post-partum phase.

If, for urgent reasons, diazepam is administered in high doses in late pregnancy or during delivery, effects on the newborn baby such as respiratory failure, hypothermia, hyperactivity, excitability, hypotension, reduced muscle tone and feeding problems (floppy infant syndrome) can be expected.

Lactation
Diazepam and its metabolic products pass into breast milk. The milk-plasma ratio shows important individual differences. As diazepam is metabolized to a significantly slower

extent in newborn babies than in children or adults, babies should not be breastfed by women under diazepam therapy. In case of an urgent indication, weaning is necessary.

4.7 Effects on ability to drive and use machines

Even in case of appropriate administration, this drug can alter the ability to reactto such an extent that the fitness to drive and the capacity to operate machines are affected. This applies even more so in combination with alcohol.
In the course of the treatment with the solution for injection as well as 24 hours after the last injection, the patient must not drive or undertake any activity through which the patient can put himself/herself or others in danger. If the solution for injection has been used for diagnostic purposes, the patient should return home only if accompanied by another person.
Consumption of alcohol during concomitant use of *Assival Teva 10 mg/2 ml solution for injection* still causes increased impairment of motor functions and of usual behaviour even 10 hours after the last dose. This can represent a considerable risk for work and traffic accidents.

4.8 Undesirable effects

The evaluation of undesirable effects is based on the following frequency data:

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
Unknown	Cannot be estimated from the available data

Undesirable effects of diazepam are frequent – depending on the individual sensitivity of the patient and the dose used, and of varying intensity, and appear primarily at the beginning of the treatment. They can often be reduced or avoided by careful individual adjustment of the daily dose or they can decrease in the course of the therapy.

Metabolic and nutritional disorders

Rare:	Appetite increase

Psychiatric disorders

Common:	Depression
Uncommon:	Change in sex drive (increased or decreased libido)

If hallucinations and psychoses occur as well as "paradoxical" reactions, such as acute states of excitation, excitability, irritability, aggressive behavior, restlessness (agitation), nervousness, hostility, anxiety states, suicidality , insomnia, rage attacks, increased muscle spasms, nightmares and vivid dreams, the treatment with diazepam should be terminated (see Section 4.4).

In patients with pre-existing depressive disorder, the symptoms can be enhanced (see Section 4.4).

Diazepam possesses a primary potential for dependency. There is a risk of dependency even with daily use over a few weeks. This applies not only to misuse intake of particularly high doses, but also to the therapeutic dose range (see Section 4.4).

When diazepam therapy is stopped, discontinuation phenomena (e.g. rebound phenomena) or withdrawal symptoms are possible (see Section 4.4).
During treatment with benzodiazepines, it should generally be taken into account that withdrawal symptoms can appear if the patient switches to a benzodiazepine with a markedly shorter elimination half-life.

Nervous system disorders

Common:	Undesirably high daytime sedation such as fatigue (somnolence, lassitude, drowsiness, delayed reaction time), sensation of dizziness, headache, ataxia, confusion, anterograde amnesia
Uncommon:	Tremor

In the morning following evening administration, hangover effects (concentration disturbances and residual fatigue) can impair the reaction capacity.

Anterograde amnesia can appear during benzodiazepine treatment with therapeutic doses. The risk of appearance of this undesirable effect increases with higher doses. Amnesic effects may be related to inappropriate behavior (see Section 4.4).

At high doses and during prolonged use of diazepam, reversible disturbances, such as slow or slurred speech (articulation disturbances) and unsteadiness of movement and gait are possible.

Eye disorders
At high doses and during prolonged use of diazepam, reversible visual disturbances (diplopia, blurred vision, nystagmus) can occur.

Ear and labyrinth disorders

Not known:	Vertigo

Cardiac disorders:

Rare:	Bradycardia
Not known:	Arrhythmia, heart failure including cardiac arrest

Vascular disorders:

Uncommon:	Hypotension, circulatory collapse

Respiratory, thoratic and mediastinal disorders

Rare:	Laryngospasm, chest pain, respiratory depression including respiratory arrest.

The respiratory depression effect can appear in a more severe form if there is airway obstruction and in patients with brain injury. This needs to be borne in mind in particular in the case of concomitant combination with other centrally acting substances(see Sections 4.4 and 4.5).

Gastrointestinal disorderss

Uncommon:	Nausea, vomiting, epigastric complaints, constipation, diarrhea, dry mouth, increased salivation.

Hepatobiliary disorders

Rare:	Jaundice

Skin and subcutaneous tissue disorders

Uncommon:	Allergic skin reaction (e.g. itching, urticaria, skin rash)

Musculoskeletal and conjunctive tissue disorders

Not known:	Muscle weakness

Renal and urinary disorders

Uncommon:	Urinary retention, incontinence

Reproductive system and breast disorders

Rare:	Menstrual cycle disorders in women

*General diorders and administration site conditions*Rarely, hypersensitivity reactions caused by benzyl alcohol can occur.

Not known	Risk of falls

In elderly patients on benzodiazepine treatment, an increased risk of falls and fractures was observed.

During long-term and repeated use of diazepam, development of tolerance is possible.

Rapid I.V. administration, can cause a fall in blood pressure, cardiac arrest and respiratory arrest by influencing cardiovascular and respiratory function.

In case of injection into a vein that is too small, irritation of the venous wall (as well as thrombophlebitis) is possible. Especially in the case of a too rapid injection, a burning sensation and pain in the area of the injection site can occur.

In rare cases, intramuscular injections can lead to irritation and pain at the injection site (see Section 4.2).

Tests

Not known	Elevated transaminase and alkali phosphatase values

The following have also appeared during treatment with benzodiazepines: EEG alterations, blood count changes including agranulocytosis, blurred vision, double vision, fever, stupor, orientation disorders and euphoria.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

In any evaluation of an intoxication, the presence of multiple intoxication by possible use of several medicinal products, for instance in suicidal intent, should be considered.

Intoxication symptoms are more severe under the influence of alcohol and/or other centrally acting medicinal products.

a) Symptoms of overdose

The symptoms of slight overdose include, for instance, confusion, somnolence, ataxia, dysarthria, hypotonia and muscle weakness.

In case of severe intoxication, central depression of the cardiovascular and respiratory function (cyanosis, loss of consciousness and even respiratory arrest, cardiac arrest) can occur (intensive monitoring required!)

In the attenuation phase, severe states of agitation are possible.

b) Therapeutic measures in case of overdose

Apart from monitoring respiration, pulse rate, blood pressure and body temperature, I.V. fluid replacement as well as supportive measures and provision of emergency measures for any possible airway obstruction are indicated in general (if necessary intensive monitoring). In case of hypotention, sympathomimetics can be administered. In respiratory failure, which can also be caused by peripheral muscle relaxation, assisted ventilation is indicated. Morphine antagonists are contraindicated.

Because of high plasmaprotein binding and the large distribution volume, forced diuresis or hemodialysis are probably of little use in pure diazepam intoxication.

N.B.:
Flumazenil is indicated for the removal of the central depressant effect of benzodiazepines. It is therefore used in the following indications:

- Termination of benzodiazepine-induced and maintained anaesthesia in inpatients

- Reversal of benzodiazepine induces sedation as part of therapeutic measures in inpatients

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anxiolytics, benzodiazepine derivates.
ATC Code: N05BA01

Diazepam is a psychotropic substance of the class of the 1,4- benzodiazepines with pronounced tension, excitation and anxiety-reducing properties as well as with sedating and hypnotic effects. Moreover, in higher doses, diazepam has depressant and anticonvulsive effects on the muscular tonus.
Diazepam binds to specific receptors in the central nervous system as well as in individual peripheral organs. The benzodiazepine receptors in the central nervous system are in close functional relation with the receptors of the GABA transmitter system. After binding to the benzodiazepine receptor, diazepam enhances the inhibiting effect of the GABA transmission.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of diazepam show great inter-individual variability.

Absorption, maximum plasma concentration
After intravenous administration of an aqueous solution for injection, maximum plasma and serum concentrations of diazepam are reached immediately after injection.
After intramuscular injection, the absorption of diazepam is slower and corresponds to that of oral administration (up to 1 hour).
Serum concentration after I.V/I.M. administration of 10 mg diazepam ranges between 250-600 ng/ml. As the plasma concentration of diazepam after a single I.V. injection decreases very quickly because of rapid distribution, repeated injection is necessary after 20-30 min.

Protein binding, volume of distribution
Plasma protein binding ranges between 95-99 %; people suffering from renal or hepatic diseases present lower values.
Depending on age, the volume of distribution varies between 0.95 and 2 l/kg body weight.

Biotransformation, elimination
The degradation of diazepam takes place mainly in the liver into the equally pharmacologically active metabolites, N-desmethyldiazepam (nordazepam), temazepam and oxazepam, which appear in the urine as glucuronides. Only 20 % of the metabolites appear in the urine in the first 72 hours.
The active metabolites have the following plasma half-lives:

N-desmethyldiazepam	30-100 h
Temazepam	10-20 h
Oxazepam	5-15 h

During repeated dosing of diazepam, the proportion of N-desmethyldiazepam prevails, with large interindividual differences. This main metabolite has a longer terminal half-life than the parent substance.

During chronic medication with diazepam, elimination is additionally prolonged by accumulation, and therapeutically relevant serum concentrations of the main metabolite appear.

The elimination of diazepam and its main metabolite from the plasma is very slow. The 1st elimination phase has a half-life of 1 h; the values obtained for the 2nd elimination phase – depending on age and hepatic function - range between 20-100 h. Excretion is mainly renal and partially biliary. It also depends on age and renal and hepatic function. The metabolism and elimination of diazepam in the newborn is considerably slower than in children and adults.
In the elderly, the elimination is slowed by a factor of 2 to 4.
In impaired renal function, the elimination is also slowed .
In patients with hepatic disorders (hepatic cirrhosis, hepatitis), the elimination is slowed by a factor of 2.

Passage into cerebro-spinal fluid
Diazepam is lipophilic and passes rapidly into cerebro-spinal fluid with its active main metabolite.

Passage into the placenta, lactation
Diazepam and its main metabolite N-desmethyldiazepam cross the placenta and are secreted in breast milk. Diazepam accumulates in the fetal compartment and in the blood of the newborn, can reach concentrations that are three times those of the maternal serum concentration.
In preterm babies elimination is delayed because of immature hepatic and renal function and can take up to 10 days.
If diazepam was given prior to or during delivery or if the mother had been administered higher doses on multiple occasions, Apgar scores are significantly lower in preterm babies and in the newborn, the frequency of hyperbilirubinemia is significantly higher, and pronounced edemas and muscle hypotonia have been observed up to 4 days after delivery.

Bioavailability
The systemic availability of diazepam after intravenous administration is 100 %; however, after intramuscular administration it is considerably lower and corresponds to that of oral administration – depending on the pharmaceutical composition, i.e. approx. 75-80 %.

5.3 Preclinical safety data

Acute toxicity
See Section 4.9.

Chronic toxicity

Studies in different animal species did not show any evidence of substance induces changes.

Mutagenicity
Several genotoxicity studies yielded weak evidence of a mutagenic potential in high concentrations, which, however, are well above the therapeutic dosage in humans.

Carcinogenicity
The carcinogenic potential of diazepam was studies in different species of rodents. In male mice, there was an increased incidence of hepatocellular carcinomas. On the other hand, no significant increase of the tumor incidence was observed in female mice, rats, hamsters or gerbils.

Reproductive toxicity
Diazepam and its main metabolite N-desmethyldiazepam cross the placenta. Diazepam accumulates in the fetal compartment and in the blood of the newborn can reach concentrations that are three times those of the maternal serum concentration. The malformation risk with use of therapeutic doses of benzodiazepines seems to be low, although some epidemiological studies have provided evidence of an increased risk of cleft palate.
Ther are case reports of malformation and intellectual disability in prenatally exposed children after benzodiazepine overdoses and intoxication (see Section 4.6).

Results of animal studies
In mice, after prenatal diazepam exposure, cases of cleft palate were noted. In hamsters, after very high prenatal diazepam doses, exencephalies and limb malformations were also noted, apart from cleft palate. In rats and primates, diazepam was not teratogenic. Animal studies have shown evidence of behavioural changes in the progeny of mothers exposed for long periods. In mice, after 1-6 weeks of treatment with diazepam, sperm head anomalies were seen.

6. PHARMACEUTICAL DATA

6.1 List of excipients
Water for injections, propylene glycol, ethanol, sodium benzoate, benzyl alcohol, benzoic acid.

6.2 Incompatibilities
Because of chemical incompatibility with other medicinal products, *Assival Teva 10 mg/2 ml solution for injection* must not be injected into the same syringe with other medicinal products or be mixed with other medicinal products in a solution for infusion.

Compatability after dilution has been demonstrated for 24 hours at 25ºC for two Assival Teva 10mg/2ml ampoules diluted with 250 ml glucose solution 5%, and for two Assival Teva 10mg/2ml ampoules diluted with 250 ml 0.9% sodium chloride solution.

PVC infusion bags should not be used. The dilution should be performed immediately before use. From a microbiological point of view, the infusion preparation should be used immediately. If not used immediately, the in-use storage times and conditions prior to use are the responsibility of the user. Dilution should take place in controlled and validated aseptic conditions.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Carton box containing 10 brown glass ampoules.
Each ampoule contains 2 ml solution.

6.6 Special precautions for disposal and other handling

No special requirements

Marketing authorization holder and manufacturer

Teva Pharmaceutical Industries Ltd., PO Box 3190 Petah Tikva

Marketing authorization number

158.53.34806

This leaflet format has been determined by the Ministry of Health and the content thereof has been checked and approved on May 2017. The leaflet was updated on August 2019 according to Ministry of Health instructions.