This leaflet format has been determined by the Ministry of Health and the content thereof has been checked and approved in May 2017

Assival® Teva 10 mg/2 ml
Solution for I.M. or I.V. Injection

1. NAME OF THE MEDICINAL PRODUCT

Assival® Teva 10 mg/2 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients include: benzyl alcohol (30 mg/2 ml), ethanol (13.12% by volume), benzoic acid, sodium benzoate.

Each ampoule contains about 15.6 mg sodium.

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 spasm, 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 should 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 who 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 one of the other ingredients mentioned in Section 6.1
- First trimester of pregnancy and in breastfeeding
- Dependency anamnesis (alcohol, medicines, drugs)
- Acute alcohol, sleeping pills, analgesics (opiates) as well as psychotropic drugs (neuroleptics, antidepressants, lithium) intoxication
- Myasthenia gravis
- Spinal and cerebral ataxia
- Severe respiratory insufficiency
- Sleep apnea syndrome
- Severe hepatic insufficiency
- 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

At the beginning of the therapy, the individual reaction of the patient to the drug should be controlled, in order to identify as soon as possible an eventual relative overdose. This applies in particular to elderly and debilitated patients, children and adolescents, as well as patients with organic brain changes, circulatory or respiratory insufficiency or with impaired hepatic or renal function. Apart from this, patients shall be given precise behavior indication for the daily life, while taking into account the specific situation (e.g., professional activity).

After ambulatory administration for diagnostic purposes, the patient should be discharged home only after 1 hour and only 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 fall hazard, 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 sole means of treatment of depressions or states of anxiety accompanied by depressions. 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 cardiac insufficiency and/or hypotension, whose response to benzodiazepines is often stronger than desired, and in patients with organic brain changes, the prescription shall be weighed carefully. 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 insufficiency because of the risk of respiratory depression (see Section 4.2).

Although a fall of the blood pressure does not occur often, Diazepam should be used carefully in patients in whom a fall of the blood pressure could cause cardiac complications. This applies in particular to elderly patients.

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

Patients with dependency on drugs with depressant action of the central nervous system, including alcohol, should not be treated with Diazepam, except in cases of acute withdrawal reaction.

Patients with volume deficiency shock may be treated with the injection form only if measures for the balancing of the volume deficiency have been taken simultaneously.

Patients in a coma may be treated with the injection form only in case of great agitation or convulsive states that have not been caused by intoxication.

In patients with allergic skin disease, increased vascular permeability, or hematopoietic disturbances 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 preexisting alcohol and barbiturate dependency, cross tolerance is possible.

Development of dependency

The use of benzodiazepines can lead to the development of mental 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 alcohol, medicine or drug dependency in the anamnesis.

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

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

Withdrawal phenomena/discontinuation symptoms

In particular upon termination of a longer treatment, discontinuation symptoms are possible. These symptoms are manifested as sleeping disorders, increased dreaming, headaches, muscular pain, anxiety, states of tension, inner unrest, 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, deafness and paresthesia in the extremities, epileptic attacks, hallucinations and symptomatic psychoses (e.g., withdrawal delirium).

The sudden termination of a shorter treatment can also cause to transient withdrawal (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 unrest are possible.

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

It is recommended that the patient be advised at the beginning of the therapy on the limited treatment period and be explained in detail the gradual diminishing of the dose. Moreover, it is important that the patient should be aware of the possibility of rebound phenomena, whereby 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 some circumstances for a period (in most cases a few hours) after use of the drug, the patient may not remember the actions that he/she has carried out.

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

Mental and "paradox" reactions

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

Children and adolescents

Treatment of children or adolescents with *Assival Teva 10 mg/2 ml solution for injection* should take place only in case of strict indication (see Section 4.2).

The safety and the effectiveness of Diazepam in children of less than 6 months of age were not examined. 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).

In infants and in children of up to 3 years of age, benzyl alcohol can cause toxic and anaphylactoid reactions.

This drug contains 13.12 vol.% alcohol.

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

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 determined by CYP3A, whereas in the N-desmethylization by both isoenzymes CYP3A and CYP2C19 are involved. These *in vitro* observations were confirmed by findings from *in vivo* studies with probands.

Drugs used concomitantly, containing active substances that are also substrates of CYP3A and/or CYP2C19 can change 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 drugs, mutual enhancement of the sedating, respiratory and hemodynamic effects is possible:

- Sedatives, hypnotics, narco-analgesics, anesthetics
- Neuroleptics
- Antiepileptics
- Anxiolytics
- Sedating antihistaminics
- Antidepressants, lithium preparations
- 4-hydroxybutane 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, the combination with narco-analgesics can cause an intensification of the euphorizing effect and thus to accelerated development of dependency.

In case of simultaneous administration of muscle relaxants, the relaxing effect is enhanced – in particular in elderly patients and with higher doses (fall hazard!).

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 must be taken into account even after the termination of the Diazepam treatment.

In patients under long-term therapy with other drugs, such as anti-hypertensives acting on the central nervous system, β-blockers, anticoagulants, cardiac glycosides, the nature and scope of the interactions are not certainly foreseeable. The treating physician should verify the existence of long-term treatments prior to the administration of Diazepam. Therefore, particular caution is required upon concomitant use of the preparation, particularly 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 longer period.

Diazepam and its main metabolite N-Desmethyldiazepam pass through the placenta. Diazepam accumulates in the fetal compartment and can reach in the blood of the newborn triple that 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 cleft palate risk.

Case reports of malformation and mental retardation of prenatally exposed children after benzodiazepine overdose and intoxications are available.

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 stringent reasons, Diazepam is administered in high doses in late pregnancy or during delivery, effects on the newborn baby such as respiratory insufficiency, hypothermia, hyperactivity, excitability, hypotension, low muscular tonus and feeding problems (floppy infant syndrome) can be expected.

Lactation

Diazepam and its metabolic products pass into the breast milk. The milk-plasma ratio shows important individual differences. As Diazepam is metabolized in a significantly slower manner in newborn babies than in children or adults, babies should not be breastfed by women under Diazepam therapy. In case of stringent indications, weaning is necessary.

4.7 Effects on ability to drive and use machines

Even in case of appropriate administration, this drug can alter the reaction capacity to such an extent that the fitness to drive and the capacity to operate machines are affected. This applies even more in interaction with alcohol.

In the course of the treatment with the solution for injection as well as 24 hours after the last injection, no vehicles must be driven and no activity by which the patient can put him/herself or others in danger must be exercised. If the solution for injection was used for diagnostic purposes, the patient should return home only accompanied by another person.

Consumption of alcohol under concomitant use of *Assival Teva 10 mg/2 ml solution for injection* leads, as late as 10 hours after the last dose, to an enhanced impairment of the motor functions and of the usual conduct. This can represent a considerable risk of work and traffic accidents.

4.8 Undesirable effects

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

Very common	≥ 1/10
Common	≥ 1/100 to < 1/10
Occasional	≥ 1/1,000 to < 1/100
Rare	≥ 1/10,000 to < 1/1,000
Very rare	< 1/10,000
Unknown	Frequency not assessable based on the available data

The side effects of Diazepam are numerous – depending on the individual sensitivity of the patient and of the dose used, with a different degree of intensity, and they appear primarily at the beginning of the treatment. They can often be minimized or avoided by individual adjustment of the daily dose or they can decrease in the course of the therapy.

Metabolic and nutritional disturbances

Rare:	Appetite increase

Psychiatric diseases

Common:	Depression
Occasional:	Alteration of the sexual urge (increase or decrease of the libido)

Upon occurrence of hallucinations and psychoses as well as of "paradox" reactions, such as acute states of unrest, excitability, irritability, aggressive behavior, agitation, nervousness, hostility, states of anxiety, suicidal tendencies, insomnia, rage attacks, increased muscular spasms, nightmares and vivid dreams, the treatment with Diazepam should be terminated (see Section 4.4).

In patients with preexisting depressive disease, the symptoms can be enhanced (see Section 4.4).

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

Upon termination of the Diazepam therapy, discontinuation phenomena (e.g., rebound phenomena) or withdrawal symptoms are possible (see Section 4.4).

In the therapy with benzodiazepines, it should be generally taken into account that withdrawal symptoms can appear if the patient switches to a benzodiazepine with a markedly shorter elimination halftime.

Diseases of the nervous system

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

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

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

In high dosage and long-term use of Diazepam, reversible disturbances, such as slow or blurred speech (articulation disturbances) and movement and gait insecurity are possible.

Ophthalmological diseases

In high dosage and long-term use of Diazepam, reversible vision disturbances (diplopia, blurred vision, nystagmus) are possible.

Ear and labyrinth diseases

Unknown:	Vertigo

Cardiac diseases

Rare:	Bradycardia
Unknown:	Arrhythmia, cardiac failure including cardiac arrest

Vascular diseases

Occasional:	Hypertension, circulatory collapse

Diseases of the respiratory ways, of the thoracic cavity and of the mediastinum

Rare:	Glottis spasms, chest pains, respiratory depression including respiratory arrest

The respiratory depression effect can appear in an intensified form in obstructions of the respiratory ways and in patients with brain damage. This shall be considered in particular in case of concomitant combination with other substances acting on the central nervous system (see Sections 4.4 and 4.5).

Gastrointestinal tract diseases

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

Liver and gall bladder diseases

Rare:	Jaundice

Skin and subcutaneous tissue diseases

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

Skeleton musculature, conjunctive tissue and bone diseases

Unknown:	Muscle weakness

Kidney and urinary tract diseases

Occasional:	Urinary retention, incontinence

Sexual organs and mammary gland diseases

Rare:	Menstrual cycle disorders in women

General diseases and complaints at the administration site

Rarely, hypersensitivity reactions caused by benzyl alcohol are possible.

Unknown:	Falling hazard

In elderly patients under benzodiazepine treatment, an increased fall and fracture risk was observed.

In long-term and repeated use of Diazepam, development of tolerance is possible.

Fast I.V. administration, through influence of the cardiovascular and respiratory function, can cause hypotension, cardiac arrest and respiratory arrest.

In case of injection into a vein that is too small, irritation of the venous wall (as well as thrombophlebitis) is possible. Burning sensation and pain in the area of the injection site can be caused primarily by too fast injection.

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

Tests

Unknown:	Increased transaminase and alkali phosphatase values

The following have also appeared under 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
http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9 Overdose

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

Intoxication symptoms are intensified under the influence of alcohol and/or other drugs with a depressant action of the central nervous system.

a) Overdose symptoms

The symptoms of light overdose include, for instance, confusion, somnolence, ataxia, dysarthria, hypotonia and myasthenia.

In case of severe intoxication, central depression of the cardiovascular and respiratory function (cyanosis, loss of consciousness up to respiratory arrest, cardiac arrest) might occur (intensive supervision!)

In the attenuation phase, high-degree states of agitation are possible.

b) Therapeutic measures in case of overdose

Apart from the control of the respiration, pulse frequency, blood pressure and body temperature, I.V. fluid replacement as well as support measures and provision of emergency measures for an eventual respiratory obstruction are indicated in general (if necessary intensive monitoring). In case of hypotonia, sympathomimetics can be administered. In respiratory insufficiency, which can also be determined by muscle relaxation, assisted ventilation is indicated.

Morphine antagonists are contraindicated.

Because of the high plasma-albumin binding and of the large distribution volume, forced diuresis or hemodialysis are probably of minimal use in pure Diazepam intoxications.

N.B.:

Flumazenil is indicated for the removal of the depressant effect of benzodiazepines on the central nervous system. It is therefore used in the following indications:

- Termination of the benzodiazepine-induced and maintained narcosis in stationary patients
- Termination of the benzodiazepine-caused sedation as part of therapeutic measures in stationary patients

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-soothing 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 with the specific receptors in the central nervous system as well as in the 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 with the benzodiazepine receptor, Diazepam enhances the inhibiting effect of the GABA transmission.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of Diazepam present great inter-individual variability.

Resorption, maximum plasma concentration

After intravenous application of an aqueous solution for injection, maximum plasma and serum concentrations of Diazepam are reached immediately after the injection.

After intramuscular injection, the resorption of Diazepam is slower and corresponds to that of oral application (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 rapidly because of fast distribution, a repeated injection is necessary after 20-30 min.

Protein binding, distribution volume

The plasma protein binding ranges between 95-99%; people suffering from renal and hepatic diseases present lower values.

Depending on age, the distribution volume 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 glucunorides. Only 20% of the metabolites appear in the urine in the first 72 hours.

The active metabolites present the following plasma halftime values:

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

In repeated doses of Diazepam, the part of N-Desmethyldiazepam prevails, with important inter-individual differences. This main metabolite has a longer terminal halftime than the mother substance.

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

The elimination of Diazepam and of its main metabolite from the plasma is very slow. The 1st elimination phase has a halftime of 1 h; the values obtained for the 2nd elimination phase – depending on age and hepatic function – range between 20-100 h. The excretion is mainly renal and partially biliary. It also depends upon age and renal function. The metabolization and elimination of Diazepam in the newborn is considerably slower than in children and adults.

In old persons, the elimination is slowed down by a factor of 2 to 4.

In impaired renal function, the elimination is also slowed down.

In patients with liver diseases (liver cirrhosis, hepatitis), the elimination is slowed down by a factor of 2.

Passage into the cerebrospinal fluid

Diazepam is lipophilic and passes rapidly into the cerebrospinal fluid with its active main metabolite.

Passage into the placenta, lactation

Diazepam and its main metabolite N-Desmethyldiazepam pass into the placenta and are secreted into breast milk. Diazepam accumulates in the fetal compartment and can reach, in the blood of the newborn, triple that of the maternal serum concentration.

In the prematurely born, because of the immature hepatic and renal function, elimination is slowed down considerably and can reach up to 10 days.

If Diazepam was given prior to or during delivery or if the mother has been administered considerably higher doses, in premature as well as in newborn babies the Apgar values are significantly lower, the frequency of hyperbilirubinemia is significantly higher, and pronounced edemas and muscular 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 oral administration – depending on the galenic composition, i.e., approx. 75-80%.

5.3 Preclinical safety data

Acute toxicity

See Section 4.9.

Chronic toxicity

Studies on different animal species did not show any evidence of substance-caused changes.

Mutagenicity

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

Carcinogenicity

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

Reproduction toxicity

Diazepam and its main metabolite N-Desmethyldiazepam pass into the placenta. Diazepam accumulates in the fetal compartment and can reach in the blood of the newborn triple that of the maternal serum 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 cleft palate risk. Case reports of malformation and mental retardation of prenatally exposed children after benzodiazepine overdose and intoxications are available (see Section 4.6).

Animal trial results

In mice, after prenatal Diazepam exposure, cases of cleft palate were noted. In hamsters, after very high prenatal Diazepam doses, exencephalies and extremity malformations were also noted, apart from cleft palate. In rats and primates, Diazepam was not teratogenic.

Animal trials have shown evidence of behavior changes in the issue of mother animal 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 the chemical incompatibility with other drugs, *Assival Teva 10 mg/2 ml solution for injection* must not be injected by mixing with other drugs in the same syringe or be mixed with other drugs in a solution for infusion.

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., P.O.Box 3190, Petah Tikva

Marketing authorization number

158.53.34806