SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lorazepam Aristo 1 mg orodispersible tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One orodispersible tablet contains 1 mg lorazepam.

Excipient with known effect

Each orodispersible tablet contains 28.5 mg lactose (as lactose monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible tablet

Lorazepam Aristo 1 mg orodispersible tablets are white to off white, circular, flat faced, bevel edged, uncoated orodispersible tablet with deep breakable score-line on one side and other side plain, diameter 6.3 mm.

The tablets can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Symptomatic short-term treatment of anxiety and insomnia caused by anxiety, where the anxiety is severe, disabling or subjecting the individual to unacceptable distress

- Premedication before diagnostic procedures or before surgical interventions

4.2 Posology and method of administration

Posology
Prior to starting treatment with lorazepam, a discussion should be held with patients to put in place a strategy for ending treatment with lorazepam in order to minimise the risk of dependence, addiction and drug withdrawal syndrome (see section 4.4).

Treatment should be given for the shortest possible duration.

The dose must be adjusted to the individual response, therapeutic indication and the severity of the illness. As a basic rule, the dose should be kept as low as possible.

Treatment of anxiety and sleep disorders caused by anxiety
The daily dose is generally 0.5 to 2.5 mg lorazepam, divided into 2 to 3 single doses or as a single evening dose. In individual cases, especially in inpatient use, the daily dose can be increased to a maximum of 7.5 mg, taking all precautions into consideration.

If the main focus involves sleep disorders requiring treatment, the daily dose (0.5 to 2.5 mg lorazepam) can be taken as a single dose approximately half an hour before bedtime.

If the daily dose is taken as single dose in the evening it should not be taken on a full stomach. Due to a delayed onset of effect and depending on the length of the sleeping period a hang-over effect might be possible during the following day (see Section 4.4).

For acute illnesses, the use of lorazepam should be limited to single doses or for a few days. For chronic illnesses, the duration of use depends on progression. After 2 weeks of daily intake, the physician should clarify by gradual dose reduction whether treatment with lorazepam is still indicated.

Premedication before diagnostic procedures or before surgical interventions
1 to 2.5 mg lorazepam on the evening before and/or 2 to 4 mg approximately 1 to 2 hours prior to the procedure.

The orodispersible tablets can be taken independently of meals.

Special populations

Elderly and debilitated patients
For elderly and debilitated patients reduce the initial dose by approximately 50 % and adjust the dosage as needed and tolerated (see section 4.4).

Patients with impaired hepatic function

In patients with moderate to mild hepatic impairment, lower doses may be adequate. The starting dose should be half the recommended adult dose. Such patients should be carefully monitored for clinical response and tolerability, and the dose should be adjusted accordingly (see section 4.4). Lorazepam is contraindicated in patients with severe hepatic insufficiency (see section 4.3).

Patients with impaired renal function
In patients with severe to mild renal impairment, lower doses may be adequate. The starting dose should be half the recommended adult dose. Such patients should be carefully monitored for clinical response and tolerability, and the dose should be adjusted accordingly (see section 4.4).

Paediatric population
Lorazepam should not be used in children and adolescents under 18 years of age, as safety and efficacy have not been established in this population, except as indicated below.

Aged less than 6 years:
Lorazepam is contraindicated in children under the age of six (see section 4.3).

Aged 6 – 12 years:
Premedication before diagnostic procedures or before surgical interventions: 0.5 mg – 1 mg, or 0.05 mg / kg body weight should not be exceeded. The dose should be taken one to two hours prior to the operation.

Aged 13 – 18 years:
Premedication before diagnostic procedures or before surgical interventions: 1–4 mg one to two hours prior to the operation.

Method of administration
Lorazepam Aristo is for oral use.
The orodispersible tablets dissolve instantly in the mouth. For swallowing, they can, if desired, be washed down with some liquid.

4.3 Contraindications

- hypersensitivity to the active substance, to other benzodiazepines or to any of the excipients listed in section 6.1.
- myasthenia gravis;
- acute intoxication with alcohol or CNS depressants (e.g. hypnotics or analgesics, neuroleptics, antidepressants and lithium);
- history of alcohol or drug dependence
- severe hepatic insufficiency (may precipitate encephalopathy)
- sleep apnoea syndrome
- severe respiratory insufficiency (e.g. chronic obstructive pulmonary disease)

- children under 6 years

4.4 Special warnings and precautions for use

At the start of therapy, the treating physician should monitor the patient's individual response to the medicinal product, so that any relative overdose can be detected as quickly as possible. This particularly applies to children, elderly patients, as well as patients with a diminished state of health. These patients may show a more sensitive response to the effect of lorazepam and should therefore be monitored more frequently during therapy.

Depression or other psychiatric disorders
Lorazepam is not intended for the primary treatment of psychotic illness or depressive disorders. In depressive patients, the possibility of emerging or worsening of depressive symptoms is to be expected. Benzodiazepine treatment can unmask suicidal tendencies in these patients; it should not be undertaken without adequate antidepressant therapy.

Suicidality
Some epidemiological studies indicate an increased incidence of suicide and suicide attempts in patients with or without depression, and treated with benzodiazepines or hypnotics, including lorazepam. However, a causal association has not been demonstrated.

Renal and hepatic impairment
Although bioavailability and metabolism of lorazepam are not significantly altered by renal dysfunction and are only significantly altered by severe hepatic dysfunction, caution should be exercised due to the observed greater sensitivity to the effect of these medicinal products; this also applies to elderly patients, who are at greater risk of falls, especially when they get up at night.
Exacerbation of hepatic encephalopathy may occur with the use of lorazepam.

Blood dyscrasia
Some patients taking benzodiazepines have developed blood dyscrasia, and some have had elevated levels of liver enzymes. Periodic haematological and hepatic function assessments are recommended where repeated courses of treatment are considered clinically necessary.

Hypotension
Although hypotension has occurred only rarely, benzodiazepines should be administered with caution in those patients in whom a drop in blood pressure may lead to cardiovascular or cerebrovascular complications; this is of particular importance in elderly patients.

Hang-over
Although lorazepam belongs to the benzodiazepines with a medium-long half-life, hang-over effects may occur, especially at higher doses and if the duration of sleep is

too short. It should therefore be ensured that sufficient sleeping time (approximately 7 to 8 hours) is available (see section 4.2).

Amnesia
Transient anterograde amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Patients should also be given precise instructions on how to go about their everyday life, taking their particular lifestyle into consideration (e.g. occupation).

Paradoxical reactions
There have been uncommon reports of paradoxical reactions occurring with the use of benzodiazepines (see section 4.8). Such reactions are to be expected especially in children and elderly people. Treatment with lorazepam should be discontinued if paradoxical reactions occur.

Respiratory depression
Potentially fatal respiratory depression may occur with use of benzodiazepines, including lorazepam.

Muscle weakness
Lorazepam can cause muscle weakness. Therefore, in patients with pre-existing muscle weakness or spinal or cerebellar ataxia special caution is required and a dose reduction may be necessary.

Acute narrow angle glaucoma
Caution should be used in the treatment of patients with acute narrow angle glaucoma.

Drug dependence, tolerance and potential for abuse
Drug addiction comprises behavioural, cognitive and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use and possible tolerance or physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, which manifests as withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Addiction and dependence are related but distinct presentations and in discussing these themes, terminology that apportion blame to the individual should be avoided.

For all patients, prolonged use of this product may lead to drug dependence and addiction but can occur with short-term use at recommended therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of drug misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of symptom control as initially experienced. Patients may also supplement their treatment with additional medications to achieve the same effect. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction.

The clinical need for treatment with clonazepam should be reviewed regularly, with frequent assessments of patients being undertaken during the course of their treatment.

Drug withdrawal syndrome

Prior to starting treatment with lorazepam, a discussion should be held with patients to explain the risk of dependence, addiction, and drug withdrawal syndrome. A withdrawal strategy for ending treatment with clonazepam should also be put in place with the patient before starting treatment (there may be exceptions to this in specific clinical situations such as symptom management in end of life palliative care).

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take in excess of weeks or months. Patients should be informed of this when the medication is first prescribed.

The reduction schedule for a patient should be tailored to the individual and should be modified to allow intolerable withdrawal symptoms to improve before making the next reduction. If using a published withdrawal schedule, apply it flexibly to accommodate the person’s preferences, changes to their circumstances and the response to dose reductions.

Suggest a slow stepwise rate of reduction proportionate to the existing dose, so that decrements become smaller as the dose is lowered, unless clinical risk is such that rapid withdrawal is needed.

If a patient develops withdrawal reactions, consider pausing the taper or increasing the dosage to the previous tapered dosage level.

If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Alcohol

Patients should be advised that since their tolerance for alcohol and other CNS depressants will be diminished in the presence of lorazepam, CNS depressants should be avoided or taken in reduced dose and alcohol should be avoided.

Risks from concomitant use with opioids:
Concomitant use of lorazepam and opioids may result in sedation, respiratory depression, coma, and death. Because of these risks, concomitant prescribing of benzodiazepines and opioids should be reserved for patients for whom alternative treatment options are not possible.
If a decision is made to prescribe lorazepam concomitantly with opioids, the lowest effective dose should be used and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).
The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers (where applicable) to be aware of these symptoms (see Section 4.5).

Anaphylactic/anaphylactoid reactions
Severe anaphylactic/anaphylactoid reactions have been reported with benzodiazepine use. Following ingestion of the first dose or subsequent doses of benzodiazepines, cases of angioedema involving the tongue, glottis or larynx have been reported. Some patients have experienced other symptoms while taking benzodiazepines, such as dyspnoea, swelling of the throat or nausea and vomiting. Some patients had to be treated as a medical emergency. If angioedema occurs with involvement of the tongue, glottis or larynx, airway occlusion may occur and may be fatal. In patients experiencing angioedema during treatment with a benzodiazepine, re-exposure to the medicinal product should not take place.

Elderly patients
Lorazepam should be used with caution in elderly due to the risk of sedation and/or musculoskeletal weakness that can increase the risk of falls, with serious consequences in this population. Elderly patients should be given a reduced dose (see section 4.2).
Elderly patients should be warned of the risk of falls.

Paediatric population
Children and adolescents under 18 years should not be treated with lorazepam, unless strictly indicated for sedation prior to diagnostic procedures, as well as before surgical procedures. For children under 6 years, lorazepam is contraindicated.

Excipients
Lorazepam Aristo contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

When lorazepam is co-administered with other CNS depressants (e.g. neuroleptics, anxiolytics, antidepressants, hypnotics/sedatives, anaesthetics, beta-blockers, opiate-type analgesics, sedative antihistamines, antiepileptics) and alcohol, the CNS-depressant effects may be mutually potentiated.

Alcohol

Concomitant alcohol intake should be avoided.

The sedative effects of lorazepam may be enhanced when the medicinal product is used in combination with alcohol. This affects the ability to drive or operate machines.

Narcotic analgesics/opioids

The concomitant use of benzodiazepines and opioids increases the risk of sedation, respiratory depression, coma, and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see Section 4.4). Enhancement of the euphoria induced by narcotic analgesics may occur with benzodiazepine use, leading to an increase in psychic dependence.

Muscle relaxants

The effect of muscle relaxants and analgesics may be potentiated.

Anticonvulsants

Concomitant administration of lorazepam and valproic acid can lead to increased plasma concentrations and reduced clearance of lorazepam. If valproic acid is co-administered, the lorazepam dose should be reduced by approximately 50 %. Phenobarbital taken concomitantly may result in an additive CNS effect.

Cytochrome P-450 enzyme inhibitors

Inhibitors (e.g. cimetidine, isoniazid; erythyromycin; omeprazole; esomeprazole) reduce clearance and may potentiate the action of benzodiazepines. Itraconazole, ketoconazole and to a lesser extent fluconazole and voriconazole are potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may increase plasma levels of benzodiazepines. The effects of benzodiazepines may be increased and prolonged by concomitant use. A dose reduction of the benzodiazepine may be required.

Inducers of cytochrome P-450 enzymes (e.g. rifampicin) may increase clearance of benzodiazepines.

Clozapine: With concomitant use of lorazepam and clozapine, marked sedation, excessive salivation and impaired coordination of movement may occur.

Loxapine*:* concomitant administration has led to reports of excessive stupor, significant reduction in respiratory rate, and in one patient, hypotension.

Antihypertensives, vasodilators and diuretics: Enhanced hypotensive effect with ACE-inhibitors, alpha-blockers, angiotensin-II receptor antagonists, calcium channel blockers, adrenergic neurone blockers, beta-blockers, moxonidine, nitrates, hydralazine, minoxidil, sodium nitroprusside and diuretics

Probenecid: Concomitant administration of lorazepam and probenecid may lead to a more rapid onset of action or a prolonged effect of lorazepam, due to a prolongation in half-life and a decrease in total clearance. If co-administered with probenecid, the lorazepam dose should be reduced by approximately 50 %.

Sodium oxybate

Concomitant use of sodium oxybate should be avoided (enhanced effects of sodium oxybate).

Theophylline/aminophylline: The use of theophylline or aminophylline can reduce the sedative effect of benzodiazepines, including lorazepam.

Other medicinal products enhancing the sedative effect of lorazepam

- Cisapride, lofexidine, nabilone, disulfiram and the muscle relaxants – baclofen and tizanidine
- Enhanced sedative effect with alpha-blockers or moxonidine.
- Dopaminergics: Possible antagonism of the effect of levodopa
- Antacids: Concurrent use may delay absorption of lorazepam
- Zidovudine: Increased zidovudine clearance by lorazepam
- Oestrogen-containing contraceptives: Possible inhibition of hepatic metabolism of lorazepam

Caffeine

Concurrent use may result in reduced sedative and anxiolytic effects of lorazepam.

Grapefruit juice

Inhibition of CYP3A4 may increase the plasma concentration of lorazepam (possible increased sedation and amnesia). This interaction may be of little significance in healthy individuals, but it is not clear if other factors such as old age or liver cirrhosis increase the risk of adverse events with concurrent use.

As the nature and extent of interactions cannot be reliably predicted in individual cases among patients on long-term treatment with other medicinal products, particular caution should be exercised, especially at the start of treatment.

4.6 Fertility, pregnancy and lactation

Pregnancy

Lorazepam should not be used during pregnancy, especially during the first and last trimesters. Benzodiazepines may cause foetal damage when administered to pregnant

women. Cases of malformation and mental retardation of prenatally exposed children after overdose and poisoning have been reported. If the medicinal product is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuance of the medicinal product if she intends to become or suspects that she is pregnant.

If, for compelling medical reasons, the medicinal product is administered during the late phase of pregnancy, or during labour at high doses, effects on the newborn infant such as hypothermia, hypotonia and moderate respiratory depression, apnoea, feeding difficulties and impaired metabolic response to cold stress ("floppy infant syndrome") can be expected due to the pharmacological action of the compound.

Moreover, infants born to mothers who took benzodiazepines chronically during the later stages of pregnancy may have developed physical dependence and may be at some risk for developing withdrawal symptoms in the postnatal period.

Breastfeeding

As lorazepam is excreted in human milk, it should not be taken during breastfeeding, unless the expected benefit for the woman outweighs the potential risk to the infant (see section 5.2). Sedation and inability to suckle have occurred in neonates of lactating mothers taking benzodiazepines Infants of breastfeeding mothers should be monitored for pharmacological effects (e.g. sedation, irritability).

4.7 Effects on ability to drive and use machines

Even when used as directed, lorazepam has a major influence on the ability to drive and use machines. This particularly applies in interaction with alcohol.

Thus, patients should refrain from driving, using machines or engaging in any other hazardous activities, until it has been shown that their responsiveness is not impaired by lorazepam. The decision should be made by the attending physician in each individual case, taking into account the individual response and the respective dosage.

4.8 Undesirable effects

Adverse reactions are to be expected especially at the start of treatment, if the dose is too high and in the patient groups mentioned in sections 4.3 and 4.4. They may resolve spontaneously during the course of further therapy and/or upon dose reduction.

The following categories are used for expressing the frequency of adverse reactions:
Very common: ≥1/10

Common: ≥1/100 to <1/10
Uncommon: ≥1/1,000 to <1/100
Rare: ≥ /10,000 to <1/1,000
Very rare: <1/10,000
Not known: cannot be estimated from the available data

Blood and lymphatic system disorders
Very rare: leucopenia
Not known: thrombocytopenia, agranulocytosis, pancytopenia

Psychiatric disorders
Drug dependence (see section 4.4)

Nervous system disorders
Benzodiazepines cause dose-dependent CNS depression.
Very common: sedation, fatigue, drowsiness
Common: ataxia, confusion, depression, unmasking of depression, dizziness
Uncommon: changes in libido, impotence, less intense orgasm
Rare: reduced alertness
Not known: prolonged response times, extrapyramidal symptoms, tremor, visual disturbances (diplopia, blurred vision), dysarthria/slurred speech, headache, convulsions/seizures, amnesia, disinhibition, euphoria, coma, suicidal thoughts/attempt, impaired attentiveness/concentration, balance disorders, vertigo paradoxical reactions, such as anxiety, states of agitation, delusion, excitability, aggressive behaviour (hostility, aggression, rage), sleep disorders/insomnia, sexual arousal, hallucinations, psychoses. If such reactions occur, treatment with Lorazepam Aristo should be terminated.

Cardiac disorders
Not known: hypotension, slight decrease in blood pressure

Respiratory, thoracic and mediastinal disorders
Not known: respiratory depression (dose-dependent in severity), apnoea, aggravation of sleep apnoea, aggravation of obstructive pulmonary disease

Gastrointestinal disorders
Uncommon: nausea
Rare: salivation changes
Not known: constipation

Hepatobiliary disorders
Not known: elevated bilirubin, jaundice, elevated liver transaminases, elevated alkaline phosphatase

Skin and subcutaneous tissue disorders
Rare: rash
Not known: allergic skin reactions, alopecia

General disorders and administration site conditions

Common: muscle weakness, lassitude

Not known: hypersensitivity reactions, anaphylactic/anaphylactoid reactions, angioedema, syndrome of inappropriate antidiuretic hormone (SIADH), hyponatraemia, hypothermia

Drug withdrawal symptoms (see 4.4 Special warnings and precautions).

Symptoms reported following discontinuation of benzodiazepines include headaches, muscle pain, anxiety, tension, depression, insomnia, restlessness, confusion, irritability, sweating, and the occurrence of "rebound" phenomena whereby the symptoms that led to treatment with benzodiazepines recur in an enhanced form. These symptoms may be difficult to distinguish from the original symptoms for which the drug was prescribed.

In severe cases the following symptoms may occur: derealisation; depersonalisation; hyperacusis; tinnitus; numbness and tingling of the extremities; hypersensitivity to light, noise, and physical contact; involuntary movements; hyperreflexia, tremor, nausea, vomiting; diarrhoea, abdominal cramps, loss of appetite, agitation, palpitations, tachycardia, panic attacks, vertigo, short-term memory loss, hallucinations/delirium; catatonia; hyperthermia, convulsions. Convulsions may be more common in patients with pre-existing seizure disorders or who are taking other drugs that lower the convulsive threshold such as antidepressants.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

As a basic rule, the possibility of multiple intoxication, e.g. ingestion of several medicinal products with suicidal intent, should always be considered. From the spontaneous reporting system, there have been known cases of overdose with lorazepam, mainly in combination with alcohol and/or other medicinal products.

Symptoms of intoxication

A benzodiazepine overdose usually manifests as CNS depression of varying degrees of severity, ranging from drowsiness to comatose states.

Symptoms of a mild overdose may include drowsiness, confusion, somnolence, lethargy, ataxia, dysarthria, paradoxical reactions, hypotonia of the muscle system and decrease in blood pressure. In cases of severe intoxication, central respiratory and circulatory depression, unconsciousness and fatalities can occur (intensive monitoring is required). In the regression phase of intoxication, severe states of agitation have

been observed.

Treatment of intoxication
Generally standard supportive and symptomatic measures are recommended; vital parameters must be monitored. Induced vomiting is not recommended if there is a risk of aspiration. Gastric lavage may be indicated if performed in good time, or in patients with symptoms of intoxication. Absorption can also be limited by administration of activated charcoal. Assisted respiration for respiratory failure. Hypotension can be treated with plasma replacement fluid.

Although in severe cases, flumazenil, a specific benzodiazepine antagonist, can be used as an antidote, this is only one component of comprehensive medical treatment of an overdose. In this regard, seizures can occur. Lorazepam is hardly removed by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nervous system; psycholeptics; anxiolytics, benzodiazepine derivatives

ATC code: N05BA06

Lorazepam is a benzodiazepine with short to medium duration of action.

Lorazepam is a psychotropic substance from the class of 1,4 benzodiazepines with anxiolytic, tension-reducing and agitation-reducing properties, as well as sedative and hypnotic effects. Furthermore, lorazepam shows myorelaxant and anticonvulsant effects.

Lorazepam has a very high affinity for specific bonding sites in the central nervous system. These benzodiazepine receptors are in close functional relation to the receptors of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). After binding to the benzodiazepine receptor, lorazepam enhances the inhibitory effect of GABAergic transmission.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, lorazepam is rapidly and almost completely absorbed. At a dose of 2 mg, the measured mean absorption half-lives vary between 10.8 and

40.4 minutes. Peak plasma levels are reached in 1 to 2 hours. After a single dose of 1 mg, the peak plasma level is about 10 to 15 ng/mL.

When 2 mg lorazepam is given orally, the value determined for bioavailability in comparison to IV administration stands at 94.1 %.

Distribution

The volume of distribution is approximately 1.3 L/kg. Data on the plasma protein binding of lorazepam, which is mainly bound to albumin, range from 80.4 to 93.2 %, which is slightly above the values of 65 to 70 % determined for the main metabolite, lorazepam glucuronide.

The concentrations of lorazepam and conjugate found in the cerebrospinal fluid are significantly lower than the concomitant plasma concentrations (on average, less than 5 % of respective plasma levels).

Lorazepam and lorazepam glucuronide pass through the placental barrier and enter the foetal circulation and amniotic fluid.

Small amounts of lorazepam and the glucuronide are excreted in breast milk. Approximately 13 % of peak maternal serum concentrations have been measured for lorazepam and approximately 20 % for the glucuronide.

Biotransformation

The main metabolite of lorazepam, which undergoes almost complete biotransformation, is the glucuronide, which has hardly any pharmacological action in animal trials.

After IM administration of 4 mg lorazepam, the concentration of the glucuronide, which is formed with a half-life of about 3.8 hours, can be measured after only a few minutes. The concentration of this metabolite reaches a plateau after 4 hours, which is maintained over about 8 hours.

Elimination

For the elimination half-life, values from 12 to 16 hours are reported in various studies. The elimination half-life determined for the glucuronide is 12.9 to 16.2 hours.

At an oral dose of 3 mg lorazepam/day, the steady-state concentration was reached after 2 to 3 days. The mean trough steady-state concentration was 25.3 ng/mL, but very marked interindividual differences were found (17.1 to 43.8 ng/mL). The comparison of half-lives measured after single administration and in the wash-out phase, respectively (14.9 hours versus 14.2 hours) shows that lorazepam neither inhibits nor induces its degradation. The accumulation ratio (AUC day 8/AUC day 1) was found to be 1.88.

After ingestion of 2 mg ^{14}C lorazepam, 87.8 % of the radioactivity was recovered in the 120-hour urine and 6.6 % in the faeces. Via the urine, less than 0.5 % of the dose is excreted as unchanged lorazepam. The main metabolite in the 120-hour urine is the glucuronide (74.5 % of the dose).

In the first days of life, the elimination half-life may be 2 to 4 times that of the maternal half-life. Apart from these first few days of life, the terminal elimination half-life does not show any significant age dependence.

Impaired renal function

Absorption, clearance and elimination of lorazepam are practically unchanged in cases of renal impairment, but elimination of the pharmacodynamically inactive glucuronide is considerably delayed. Biliary elimination increases with increasing impairment of renal function and accumulation of the lorazepam glucuronide.

Haemodialysis had practically no effect on the pharmacokinetics of unconjugated lorazepam, but the inactive glucuronide was removed from the plasma to a significant degree.

Impaired hepatic function

Clearance of lorazepam is not significantly altered by hepatic disorders (hepatitis, cirrhosis). However, severe hepatic dysfunction may lead to a prolongation of the terminal half-life.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity and carcinogenic potential. Lorazepam did not show a teratogenic potential and did not impair fertility in reproduction toxicity studies in rabbits, rats and mice. However, behavioural disturbances were noted in the offspring following long-term benzodiazepine exposure of the dams.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Mannitol

Microcrystalline cellulose

Polacrilin potassium

Crospovidone

Sucralose

Orange flavouring

Magnesium stearate [vegetable]

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

After dividing of orodispersible tablets: Store any remaining half orodispersible tablet in the original package in order to protect from light and moisture. Use within 24 hours.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package, in order to protect from light and moisture.

6.5 Nature and contents of container

Al/Al/LDPE

Lorazepam Aristo is available in packs, each containing 20, 25, 28, 30, 40, 50, 60 or 500 orodispersible tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Aristo Pharma GmbH

Wallenroder Strasse 8-10,

13435 Berlin,

Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 40546/0053

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/11/2025

10 DATE OF REVISION OF THE TEXT

06/03/2026