L-Asparaginase for Injection 5000 IU

ASPARAWEM
5000IU Injection

Composition :
Each vial contains :
L-Asparaginase 5000 IU
Excipients q.s.

Pharmacology
Asparaginase hydrolyses asparagine to aspartic acid and ammonia. In contrast to normal cells, lymphoblastic tumour cells have a very limited capacity for synthesising asparagine because of a significantly reduced expression of asparagine synthetase. Therefore, they require asparagine which diffuses from the extracellular environment. As a result of asparaginase-induced asparagine depletion in serum, protein synthesis in lymphoblastic tumour cells is disturbed while sparing most normal cells. Asparaginase may also be toxic to normal cells that divide rapidly and are dependent to some degree on exogenous asparagine supply.
Due to the asparagine concentration gradient between the extra- and intravascular space, asparagine levels are subsequently also reduced in the extravascular spaces, e.g. the cerebrospinal fluid.
Asparaginase is not absorbed by the gastrointestinal tract, thus L-asparaginase must be given intravenously.
Asparaginase is distributed mainly within the intravascular space. The mean (Standard Deviation, SD) of the volume of distribution at steady state (V_{dss}) was 2.47 l (0.45 l).
Asparaginase does not seem to penetrate the blood-brain barrier in measurable amounts.
Median (range) maximum serum concentrations of asparaginase activity were 2,324 U/l (1,625-4,819 U/l). Peak (Cmax) of asparaginase activity in serum was reached with a delay of approximately 2 hours after the end of the infusion.
After repeated administration of asparaginase at a dose of 5,000 U/m2 every third day, trough asparaginase activity levels in serum ranged from 108 to 510 U/l.
The metabolism of asparaginase is not known but thought to occur via degradation within the reticulo-histiocytic system and by serum proteases.
The mean ± SD terminal half-life (elimination half-life) of asparaginase activity in serum was 25.8 ± 9.9 h, with a range between 14.2 and 44.2 h.

Therapeutic indications
L-asparaginase is indicated as a component of antineoplastic combination therapy for the treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years and adults.

Posology and method of administration
L-asparaginase should be prescribed and administered by physicians and healthcare personnel experienced in the use of antineoplastic products. It should only be given in a hospital setting where appropriate resuscitation equipment is available.
Posology
L-asparaginase is usually employed as part of combination chemotherapy protocols with other antineoplastic agents.
Adults and children older than 1 year
The recommended intravenous dose of asparaginase is 5,000 units per square metre (U/m^2) body surface area (BSA) given every third day.
Treatment may be monitored based on the trough serum asparaginase activity measured three days after administration of L-asparaginase. If asparaginase activity values fail to reach target levels, a switch to a different asparaginase preparation could be considered.
Children 0 – 12 months old
Based on limited data, the recommended dose in infants is as follows:

- age less than 6 months:	6,700 U/m^2 BSA,
- age 6 – 12 months:	7,500 U/m^2 BSA.

Data on efficacy and safety of L-asparaginase in adults are limited.
Data on efficacy and safety of L-asparaginase in the post-induction treatment phases are very limited.
Special populations
Renal impairment
No dose adjustment is necessary in patients with renal impairment.
Hepatic impairment
No dose adjustment is necessary in patients with mild to moderate hepatic impairment. However, L-asparaginase should not be used in patients with severe hepatic impairment.
Elderly
Limited data are available for the treatment of patients older than 65 years of age.
Method of administration
L-asparaginase is for administration by intravenous infusion only.
needed per patient can be diluted in a final volume of 50 L 250 ml sodium The daily amount of asparaginase chloride 9 mg/ml (0.9%) solution for infusion. The diluted solution of asparaginase may be infused over 0.5 to 2 hours.
Asparaginase must not be administered as a bolus dose.

Contraindications
• Hypersensitivity to the active substance, any native (non pegylated) E. coli-asparaginase preparation.
• Pancreatitis.
• Severe hepatic impairment (bilirubin > 3 times upper limit of normal [ULN]; transaminases > 10 times ULN).
• Pre-existing known coagulopathy (e.g. haemophilia).
• History of pancreatitis, serious haemorrhage or serious thrombosis with prior asparaginase therapy.

Special warnings and precautions for use
Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should clearly be recorded.
General information and monitoring
The following life threatening situations may arise during asparaginase treatment in patients of all age groups:
• acute pancreatitis,
• hepatotoxicity,
• anaphylaxis,
• coagulation disorders including symptomatic thrombosis related to the use of central venous catheters,
• hyperglycaemic conditions.
Before initiating therapy bilirubin, hepatic transaminases and coagulation parameters (e.g. partial thromboplastin time [PTT], prothrombin time [PT], antithrombin III and fibrinogen) should be determined.
After administration of any asparaginase preparation, close monitoring of bilirubin, hepatic transaminases, blood/urinary glucose, coagulation parameters (e.g. PTT, PT, antithrombin III, fibrinogen and D-dimer), amylase, lipase, triglycerides and cholesterol is recommended.
Acute pancreatitis
Treatment with asparaginase should be discontinued in patients developing acute pancreatitis. Acute pancreatitis has developed in less than 10% of patients. In rare cases, haemorrhagic or necrotising pancreatitis occurs. There have been isolated reports of fatal outcomes. Clinical symptoms include abdominal pain, nausea, vomiting and anorexia. Serum amylase and lipase are usually elevated, although in some patients they can be normal due to impaired protein synthesis. Patients with severe hypertriglyceridaemia are at increased risk of developing acute pancreatitis.
These patients should no longer be treated with any asparaginase preparation.
Hepatotoxicity
In rare cases severe liver impairment has been described, including cholestasis, icterus, hepatic necrosis and hepatic failure with fatal outcome. Liver parameters should be monitored closely before and during treatment with asparaginase.
Treatment with asparaginase should be interrupted if patients develop severe hepatic impairment (bilirubin > 3 times the upper limit of normal [ULN]; transaminases > 10 times ULN), severe hypertriglyceridaemia, hyperglycaemia or coagulation disorder (e.g. sinus vein thrombosis, severe bleeding).
Allergy and anaphylaxis
Because of the risk of severe anaphylactic reactions asparaginase should not be administered as a bolus intravenous injection.
A previous intracutaneous test or a small intravenous test dose can be used. Both procedures, however, do not allow for predicting accurately which patients will experience an allergic reaction.
If allergic symptoms occur, administration of asparaginase must be discontinued immediately and appropriate treatment given, which may include antihistamines and corticosteroids.
Coagulation disorders
Due to the inhibition of protein synthesis (decreased synthesis of factors II, V, VII, VIII, and IX, proteins C and S, antithrombin III [AT III]) caused by asparaginase, coagulation disorders can occur which can manifest either as thrombosis, disseminated intravascular coagulation (DIC), or bleeding. The risk of thrombosis seems to be higher than the risk of bleeding. Symptomatic thromboses related to the use of central venous catheters have been described, too.
Approximately half of the thrombotic events is localised in cerebral vessels. Sinus vein thrombosis can occur. Ischaemic strokes are rare.
Acquired or genetically decreased physiologic coagulation inhibitors (protein C, protein S, antithrombin) are also described in relation to vascular complications.
Frequent evaluation of coagulation parameters is important before and during asparaginase treatment. Expert advice should be sought in cases where AT III is decreased.
Hyperglycaemic conditions
Asparaginase may induce hyperglycaemia as a consequence of decreased insulin production. Additionally it may decrease insulin secretion from pancreatic β-cells and impair insulin receptor function. The syndrome is generally self-limiting. However, in rare cases it can result in diabetic ketoacidosis. Concomitant treatment with corticosteroids contributes to this effect. Serum and urine glucose levels should be regularly monitored and managed as clinically indicated.
Antineoplastic agents
Asparaginase-induced tumour cell destruction may release large amounts of uric acid, resulting in hyperuricaemia. Co-administration of other antineoplastic medicinal products contributes to this effect. Aggressive alkalinisation of the urine and use of allopurinol can prevent urate nephropathy.
Glucocorticoids
A higher risk of thrombosis during induction therapy with asparaginase and prednisone was seen in children with a genetic prothrombotic risk factor (factor V G1691A-mutations, prothrombin G20210A-variation, methylenetetrahydrofolate reductase [MTHFR] T677T-genotype, increased lipoprotein A, hyperhomocysteinaemia).
Contraceptives
Effective contraception must be used during treatment and for at least 3 months after asparaginase discontinuation. Since an indirect interaction between components of the oral contraception and asparaginase cannot be ruled out, oral contraceptives are not considered sufficiently safe in such clinical situation.
Philadelphia chromosome-positive patients
Efficacy and safety of L-asparaginase have not been established in Philadelphia chromosome-positive patients.
Recommended control examinations for patients of all age groups
Asparaginase activity
Measurement of the asparaginase activity level in serum or plasma may be undertaken in order to rule out accelerated reduction of asparaginase activity. Preferably, levels should be measured three days after the last asparaginase administration, i.e. usually directly before the next dose of asparaginase is given. Low asparaginase activity levels are often accompanied by the appearance of anti-asparaginase antibodies. In such cases, a switch to a different asparaginase preparation should be considered. Expert advice should first be sought.
Hypoalbuminaemia
As a result of impaired protein synthesis, the serum protein level (especially albumin) decreases very commonly in patients treated with asparaginase. Since serum protein is important for the binding and transport function of some active substances, the serum protein level should be monitored regularly.
Hyperammonaemia
Plasma ammonia levels should be determined in all patients with unexplained neurologic symptoms or severe and prolonged vomiting. In case of hyperammonaemia with severe clinical symptoms, therapeutic and pharmacological measures that rapidly reduce plasma ammonia levels (e.g. protein restriction and haemodialysis), reverse catabolic states and increase removal of nitrogen wastes should be initiated and expert advice sought.
Reversible posterior leukoencephalopathy syndrome
Reversible posterior leukoencephalopathy syndrome (RPLS) may occur rarely during treatment with any asparaginase. This syndrome is characterised in magnetic resonance imaging (MRI) by reversible (from a few days to months) lesions/oedema, primarily in the posterior region of the brain. Symptoms of RPLS essentially include elevated blood pressure, seizures, headaches, changes in mental state and acute visual impairment (primarily cortical blindness or homonymous hemianopsia). It is unclear whether the RPLS is caused by asparaginase, concomitant treatment or the underlying diseases.
RPLS is treated symptomatically, including measures to treat any seizures. Discontinuation or dose reduction of concomitantly administered immunosuppressive medicinal products may be necessary. Expert advice should be sought.

Interaction with other medicinal products and other forms of interaction
General
Asparaginase may increase the toxicity of other medicinal products through its effect on liver function, e.g. increased hepatotoxicity with potentially hepatotoxic medicinal products, increased toxicity of medicinal products metabolised by the liver or bound to plasma proteins and altered pharmacokinetics and pharmacodynamics of medicinal product bound to plasma proteins. Therefore, caution should be exercised in patients receiving other medicinal products metabolised by the liver.
Hepatic parameters should be monitored when potentially hepatotoxic medicinal products are given concomitantly with asparaginase.
Myelosuppressive agents
During treatment with asparaginase-containing regimens, myelosuppression, potentially affecting all three myeloid cell lineages (erythrocytes, leukocytes, thrombocytes), and infections can occur. Concomitant treatment with myelosuppressive medicinal products and those known to cause infections are major contributing factors and patients should be carefully monitored for signs and symptoms of myelosuppression and infection.
Vincristine
The toxicity of vincristine may be additive with that of asparaginase if both agents are administered concomitantly. Therefore, vincristine should be given 3 to 24 hours before administration of asparaginase in order to minimise toxicity.
Glucocorticoids and/or anticoagulants
Concomitant use of glucocorticoids and/ or anticoagulants with asparaginase may increase the risk of a change in coagulation parameters.
This can promote tendency to bleeding (anticoagulants) or thrombosis (glucocorticoids). Caution is therefore needed when anticoagulants (e.g. coumarin, heparin, dipyridamole, acetylsalicylic acid or nonsteroidal anti-inflammatory medicinal products) or glucocorticoids are given at the same time.
Methotrexate (MTX)
Inhibition of protein synthesis secondary to the asparaginase-induced depletion of asparagine has been shown to attenuate the cytotoxic effect of MTX which requires cell replication for its antineoplastic activity. This antagonism is observed if asparaginase is administered prior to or concurrently with methotrexate. Conversely, the antitumour effects of methotrexate are enhanced when asparaginase is administered 24 hours following methotrexate treatment. This regimen has been shown to reduce the gastrointestinal and haematological effects of methotrexate.
Cytarabine
Laboratory *in vitro* and *in vivo* data indicate that the efficacy of high-dose cytarabine is reduced by prior administration of asparaginase. However, when asparaginase was given after cytarabine a synergistic effect was observed. This effect was most prominent with a treatment interval of about 120 hours.
Vaccination
Concomitant vaccination with live vaccines increases the risk of serious infection. Immunisation with live vaccines should therefore take place at the earliest 3 months after completion of the course of antileukaemic treatment.

Fertility, pregnancy and lactation
Women of childbearing potential/Contraception in males and females
Women of childbearing potential have to use effective contraception and avoid becoming pregnant while being treated with asparaginase-containing chemotherapy. Since an indirect interaction between components of the oral contraception and asparaginase cannot be ruled out, oral contraceptives are not considered sufficiently safe in such clinical situation. A method other than oral contraceptives should be used in women of childbearing potential. Men should use effective contraceptive measures and be advised to not father a child while receiving asparaginase. The time period following treatment with asparaginase when it is safe to become pregnant or father a child is unknown. As a precautionary measure it is recommended to wait for three months after completion of treatment. However, treatment with other chemotherapeutic agents should also be taken into consideration.
Pregnancy
There are no data on the use of asparaginase in pregnant women. No reproduction studies in animals with asparaginase were performed but studies with asparaginase preparations in mice, rats, chicken and rabbits have shown embryotoxic and teratogenic effects. Based on results from animal studies and its mechanism of action, L-asparaginase should not be used during pregnancy unless the clinical condition of the woman requires treatment with asparaginase.
Breast-feeding
It is unknown whether asparaginase is excreted into human breast milk. Because potential serious adverse reactions may occur in breast-feeding infants, L-asparaginase should be discontinued during breast-feeding.
Fertility
No human data on the effect of asparaginase on fertility are available.

Effects on ability to drive and use machines
L-asparaginase has moderate influence on the ability to drive and use machines, especially through its potential effects on the nervous and gastrointestinal systems.

Undesirable effects
Summary of the safety profile
The primary toxicity of asparaginase results from immunologic reactions caused by exposure to the bacterial protein. Hypersensitivity reactions range from transient flushing or rash and urticaria to bronchospasm, angioedema and anaphylaxis.
In addition, treatment with asparaginase can result in disturbances in organ systems which exhibit a high level of protein synthesis. Decreased protein synthesis can predominantly lead to liver impairment, acute pancreatitis, decreased insulin production with hyperglycaemia, decreased production of clotting factors (especially fibrinogen and antithrombin III) leading to coagulation disorders (thrombosis, bleeding), and decreased production of lipoproteins resulting in hypertriglyceridaemia.

Most serious adverse reactions of L-asparaginase include severe hypersensitivity reactions such as anaphylactic shock (rare), thromboembolic events (common), acute pancreatitis (common), and severe hepatotoxicity, e.g. jaundice, hepatic necrosis, hepatic failure (rare).
Most frequently (very common) observed adverse reactions of L-asparaginase include hypersensitivity reactions, hyperglycaemia, hypoalbuminaemia, nausea, vomiting, diarrhoea, abdominal pain, oedema, fatigue, and change in laboratory parameters (e.g. transaminases, bilirubin, blood lipids, coagulation parameters).
Since L-asparaginase is usually used in combination therapy with other antineoplastic agents, the demarcation from undesirable effects of other medicinal products is often difficult.

Tabulated list of adverse reactions

The following adverse reactions, listed in table 1, have been accumulated from clinical trials with L-asparaginase in 125 children with newly diagnosed acute lymphoblastic leukaemia as well as post-marketing experience with other *E. coli*-derived asparaginase preparations in children and adults.
Adverse reactions are ranked under headings of frequency, the most frequent first. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.
Frequencies in this table are defined using the following convention:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 1

System organ class	Frequency and adverse reaction
Infections and infestations	**Not known** Infections
Blood and lymphatic system disorders	**Common** Disseminated intravascular coagulation (DIC), anaemia, leukopenia, thrombocytopenia
Immune system disorders	**Very common** Hypersensitivity including flushing, rash, hypotension, oedema/angioedema, urticaria, dyspnoea **Common** Hypersensitivity including bronchospasm **Rare** Anaphylactic shock
Endocrine disorders	**Very rare** Secondary hypothyroidism, hypoparathyroidism
Metabolism and nutrition disorders	**Very common** Hyperglycaemia, hypoalbuminaemia **Common** Hypoglycaemia, decreased appetite, weight loss **Uncommon** Hyperuricaemia, hyperammonaemia **Rare** Diabetic ketoacidosis
Psychiatric disorders	**Common** Depression, hallucination, confusion
Nervous system disorders	**Common** Neurological signs and symptoms including agitation, dizziness and somnolence **Uncommon** Headaches **Rare** Ischaemic stroke, reversible posterior leukoencephalopathy syndrome (RPLS), convulsion, disturbances in consciousness including coma **Very rare** Tremor
Vascular disorders	**Common** Thrombosis especially cavernous sinus thrombosis or deep vein thrombosis, haemorrhage
Gastrointestinal disorders	**Very common** Diarrhoea, nausea, vomiting, abdominal pain **Common** Acute pancreatitis **Rare** Haemorrhagic pancreatitis, necrotising pancreatitis, parotitis **Very rare** Pancreatitis with fatal outcome, pancreatic pseudocyst
Hepatobiliary disorders	**Rare** Hepatic failure with potentially fatal outcome, hepatic necrosis, cholestasis, jaundice **Not known** Hepatic steatosis
General disorders and administration site conditions	**Very common** Oedema, fatigue **Common** Pain (back pain, joint pain)
Investigations	**Very common** Increase in transaminases, blood bilirubin, blood alkaline phosphatase, blood cholesterol, blood triglyceride, very low density lipoprotein (VLDL), lipoprotein lipase activity, blood urea, ammonia, blood lactate dehydrogenase (LDH), Decrease in antithrombin III, blood fibrinogen, blood cholesterol, low density lipoprotein (LDL), total protein **Common** Increase in amylase, lipase, abnormal electroencephalogram (EEG) (reduced alpha wave activity, increased theta and delta wave activity)

Description of selected adverse reactions

Immune system disorders

L-asparaginase can induce antibodies of different immunoglobulin classes (IgG, IgM, IgE). These antibodies may induce clinical allergic reactions, inactivate the enzymatic activity or accelerate the elimination of asparaginase.
Allergic reactions can manifest as flushing, rash, pain (joint pain, back pain and abdominal pain), hypotension, oedema/angioedema, urticaria, dyspnoea, bronchospasm up to anaphylactic shock.
The probability of the occurrence of allergic reactions increases with the number of administered doses; however, in very rare cases reactions can occur at the first dose of asparaginase. Most hypersensitivity reactions to asparaginase are observed during subsequent treatment phases (re-induction treatment, delayed intensification).
In a clinical trial in children with newly diagnosed ALL (study MC-ASP.5/ALL), the following frequencies of allergic events were observed (table 2).

Table 2: Frequency of patients with allergic reactions (MC-ASP.5/ALL; Safety analysis set)

Treatment group	L-asparaginase	Reference asparaginase
Number of patients	97	101
Allergic reactions within 12 hours after asparaginase infusion during induction treatment	2 (2.1%)	5 (5.0%)
Any allergic event* within 24 hours after asparaginase infusion during induction treatment	16 (16%)	24 (24%)
**Including all allergic reactions within 12 hours after asparaginase infusion and all adverse events with CTCAE terms syncope (fainting), hypotension, rash, flushing, pruritus, dyspnoea, injection site reaction or airway obstruction within 24 hours after asparaginase infusion*		

No allergic reactions were observed in any of the 12 infants < 1 year of age during treatment with L-asparaginase (study MC-ASP.6/INF).
In case of occurrence of allergic symptoms, administration of L-asparaginase should be discontinued immediately.

Immunogenicity

In the study in children/adolescents aged 1–18 years with *de novo* ALL (study MC-ASP.5/ALL), by day 33 of induction treatment 10 patients in the L-asparaginase group (10.3%) and 9 in the reference group (8.9%) were measured positive for anti-asparaginase antibodies at least at one time point.
A comparable proportion of patients in both groups developed anti-asparaginase antibodies before the start of the post-induction treatment phase (L-asparaginase 54.6% vs. reference *E. coli*-asparaginase 52.5%). The majority of anti-asparaginase antibodies developed in the time gap between the last asparaginase infusion on day 33 and start of post-induction treatment at day 79.
No anti-asparaginase antibodies were detected in any of the 12 infants < 1 year of age during treatment with L-asparaginase (study MC-ASP.6/INF).

Hypothyroidism

There have been reports of transitory secondary hypothyroidism probably caused by a decrease in the serum thyroxin-binding globulin due to asparaginase-induced protein synthesis inhibition.

Hypoalbuminaemia

As a result of impaired protein synthesis, the serum protein level (especially albumin) decreases very commonly in patients treated with asparaginase. As a consequence of hypoalbuminaemia oedema can occur.

Dyslipidemia

Mild to moderate changes in blood lipid values (e.g. increased or decreased cholesterol, increased triglyceride, increased VLDL fraction and decreased LDL, increased lipoprotein lipase activity) are very commonly observed in patients treated with asparaginase, which in most cases present without clinical symptoms. Concomitant administration of glucocorticoids may be a contributing factor. However, in rare cases severe hypertriglyceridaemia (triglycerides > 1,000 mg/dl) has been reported which increases the risk of development of acute pancreatitis. Asparaginase-associated hyperlipidaemia should be treated depending on its severity and on clinical symptoms.

Hyperammonaemia

Hyperammonaemia has been reported uncommonly in patients treated with asparaginase-containing therapy protocols, especially if patients suffer additionally from hepatic impairment. In very rare cases, severe hyperammonaemia has been reported which may induce neurologic disorders such as seizures and coma.

Hyperglycaemia and hypoglycaemia

Changes in endocrine pancreatic function are observed very commonly during treatment with asparaginase and manifest predominantly as hyperglycaemia. These events are usually transient.
In rare cases, diabetic ketoacidosis has been reported.
Hypoglycaemia mostly without clinical symptoms has been commonly observed in patients treated with asparaginase. The mechanism leading to this reaction is unknown.

Nervous system disorders

Adverse central nervous system reactions observed in patients treated with asparaginase-containing therapy protocols include changes in EEG, seizures, dizziness, somnolence, coma and headache.
The causes of these nervous system disorders are unclear. Hyperammonaemia and sinus vein thrombosis may need to be excluded.
In rare cases, RPLS has been observed during therapy with asparaginase-containing regimens.

Gastrointestinal disorders

Nausea/vomiting are very commonly observed in patients treated with asparaginase-containing treatment regimens but are usually mild. Anorexia, loss of appetite, abdominal cramps, diarrhoea and weight loss have also been reported.
Acute pancreatitis has developed in less than 10% of patients. In rare cases, haemorrhagic or necrotising pancreatitis occurs. There have been isolated reports of fatal outcomes. A few cases of asparaginase-induced parotitis have been reported in the literature.

Paediatric population

Data on safety of L-asparaginase in infants < 1 year of age is limited.

Adults and other special populations

Qualitatively, the same asparaginase-induced adverse drug reactions are observed in adults and children; however, some of these undesirable effects (e.g. thromboembolic events) are known to occur with a higher frequency in adult patients compared to the paediatric population.
Because of a higher frequency of comorbidities such as liver and/or renal impairment, patients > 55 years of age usually tolerate asparaginase treatment worse than paediatric patients.

Overdose

No case of asparaginase overdose with clinical symptoms has been reported. There is no specific antidote. Treatment is symptomatic and supportive.

Storage Condition :

Storage : Store the vials in the original carton between 2°C to 8°C

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