SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

HAMSYL® (pegaspargase) Injection 3750 International Units per 5 millilitre (3750 IU/5 ml)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml vial contains pegaspargase (pegylated L-asparaginase) 3750 IU. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/infusion.

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Hamsyl is indicated as a component of antineoplastic combination therapy in acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years, and adult patients.

4.2. Posology and method of administration

Hamsyl should be prescribed and administered by physicians and/or health care personnel experienced in the use of antineoplastic products. It should only be given in a hospital setting where appropriate resuscitation equipment is available. Patients should be closely monitored for any adverse reactions throughout the administration period.

Posology

Hamsyl is usually administered as part of combination chemotherapy protocols with other antineoplastic agents.

Recommended premedication

Premedicate patients with paracetamol, an H-1 receptor blocker (e.g. diphenhydramine), and an H-2 receptor blocker (e.g. famotidine) 30-60 minutes prior to administration of Hamsyl to decrease the risk and severity of both infusion and hypersensitivity reactions (see section 4.4). Paediatric patients and adults ≤ 21 years

The recommended dose in patients with a body surface area (BSA) ≥0.6 m^2 and who are ≤ 21 years of age is 2500 IU of pegaspargase (equivalent to 3.3 ml pegaspargase)/m^2 body surface area every 14 days.

Children with a body surface area <0.6 m^2 should receive 82.5 IU of pegaspargase (equivalent to 0.1 ml pegaspargase)/kg body weight every 14 days.

Adults >21 years

Unless otherwise prescribed, the recommended posology in adults aged >21 years is 2000 IU of pegaspargase (equivalent to 2.67 ml pegaspargase)/m^2 body surface area every 14 days.

Treatment may be monitored based on the trough serum asparaginase activity measured before the next administration of pegaspargase. If asparaginase activity values fail to reach target levels, a switch to a different asparaginase preparation could be considered (see section 4.4).

Special populations

Renal impairment

As pegaspargase is a protein with a high molecular weight, it is not excreted renally, and no dose adjustment is necessary in patients with renal impairment.

Hepatic impairment

No dose adjustment is necessary in patients with hepatic impairment.

Elderly

There are limited data available for patients older than 65 years.

Method of administration

Pegaspargase can be given by intramuscular injection or intravenous infusion.

For smaller volumes, the preferred route of administration is intramuscular. When pegaspargase is given by intramuscular injection the volume injected at one site should not exceed 2 ml in children and adolescents and 3 ml in adults. If a higher volume is given, the dose should be divided and given at several injection sites.

Intravenous infusion of pegaspargase is usually given over a period of 1 to 2 hours in 100 ml sodium chloride 9 milligram per ml (0.9%) solution for injection or 5% glucose solution.

The diluted solution can be given together with an already-running infusion of either sodium chloride 9 milligram per ml or 5% glucose. Do not infuse other medicinal products through the same intravenous line during administration of pegaspargase.

For instructions on reconstitution and dilution of this medicinal product before administration, see section 6.6.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Severe hepatic impairment (bilirubin > 3 times upper limit of normal [ULN]; transaminases > 10 times ULN).
- History of serious thrombosis with prior L-asparaginase therapy.
- History of pancreatitis, including pancreatitis related to previous L-asparaginase therapy (see section 4.4).
- History of serious hemorrhagic events with prior L-asparaginase therapy (see section 4.4).

4.4. 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 be clearly recorded.

Asparaginase antibodies

The presence of anti-asparaginase antibodies may be associated with low asparaginase activity levels due to potential neutralising activity of these antibodies. In such cases, a switch to a different asparaginase preparation should be considered.

Measurement of the asparaginase activity level in serum or plasma may be undertaken in order to rule out an accelerated reduction of asparaginase activity.

Hypersensitivity

Hypersensitivity reactions to pegaspargase, including life-threatening anaphylaxis, can occur during the therapy, including in patients with known hypersensitivity to *E. coli*-derived asparaginase formulations.Other hypersensitivity reactions can include angioedema, lip swelling, eye swelling, erythema, decreased blood pressure, bronchospasm, dyspnoea, pruritus and rash.

Premedicate patients 30-60 minutes prior to administration of pegaspargase (see section 4.2). As a routine precautionary measure the patient should be monitored for an hour after administration, resuscitation equipment and other appropriate means for the treatment of anaphylaxis should be available (epinephrine, oxygen, intravenous steroids etc.). Pegaspargase should be discontinued in patients with serious hypersensitivity reactions (see sections 4.3 and 4.8). Depending on the severity of the symptoms, administration of antihistamines, corticosteroids and vasopressors may be indicated as a counter-measure.

Pancreatic effects

Pancreatitis, including haemorrhagic or necrotising pancreatitis with fatal outcome, has been reported in patients receiving pegaspargase.

Patients should be informed of the signs and symptoms of pancreatitis which, if left untreated, could become fatal.

If pancreatitis is suspected, pegaspargase should be discontinued; if pancreatitis is confirmed, pegaspargase should not be restarted.

Serum amylase and/or lipase levels should be monitored frequently to identify early signs of pancreatic inflammation.

Blood glucose levels should be monitored, as impaired glucose tolerance may occur with concomitant use of pegaspargase with prednisone.

Coagulopathy

Serious thrombotic events, including sagittal sinus thrombosis can occur in patients receiving pegaspargase (see section 4.8). Pegaspargase should be discontinued in patients with serious thrombotic events.

Increased prothrombin time (PT), increased partial thromboplastin time (PTT), hypofibrinogenemia and antithrombin III decrease can occur in patients receiving pegaspargase. Coagulation parameters should be monitored at baseline and periodically during and after treatment; particularly when other medicinal products with anticoagulant effects (such as acetylsalicylic acid and nonsteroidal anti-inflammatory medicinal products) are used simultaneously (see section 4.5), or when concomitant chemotherapy regimen including methotrexate, daunorubicin, corticosteroids is administered. When there is a marked decrease in fibrinogen or antithrombin III (ATIII) deficiency, consider appropriate replacement therapy.

Osteonecrosis

In the presence of glucocorticoids, osteonecrosis (avascular necrosis) is a possible complication of hypercoagulability observed in children and adolescents with a higher incidence seen in girls (see sections 4.5 and 4.8). Therefore, a close monitoring in children and adolescent patients is recommended in order to detect any clinical signs/symptoms of osteonecrosis. Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment as per standard guidelines of treatment of ALL and supportive care principles.

Hepatic effects

Combination therapy with pegaspargase and other hepatotoxic products can result in severe hepatic toxicity.

Caution is required when pegaspargase is given in combination with hepatotoxic products, especially if there is pre-existing hepatic impairment. Patients should be monitored for changes in liver function parameters.

There may be an increased risk of hepatotoxicity in Philadelphia chromosome positive patients, for whom treatment with tyrosine kinase inhibitors (e.g., imatinib) is combined with L-asparaginase therapy. This should be taken into account when considering the use of pegaspargase in this patient populations.

Hepatic veno-occlusive disease (VOD), including severe, life-threatening and potentially fatal cases have been observed in patients treated with pegaspargase in combination with standard chemotherapy, including during the induction phase of multiphase chemotherapy (see section 4.8).

Signs and symptoms of VOD include rapid weight gain, fluid retention with ascites, hepatomegaly, thrombocytopenia and rapid increase of bilirubin. The identification of risk factors like pre-existing liver disease or history of VOD is essential for its prevention. Prompt recognition and appropriate management of VOD remain imperative. Patients who experience this condition should be treated according to standard medical practice.

Due to the risk of hyperbilirubinaemia, it is recommended to monitor bilirubin levels at baseline and prior to each dose.

Central nervous system effects

Combination therapy with pegaspargase can result in central nervous system toxicity. Cases of encephalopathy (including

reversible posterior leukoencephalopathy syndrome) have been reported (see section 4.8).

Pegaspargase may cause central nervous system signs and symptoms manifesting as somnolence, confusion, convulsions. Patients should be closely monitored for such symptoms, especially if pegaspargase is used in association with neurotoxic products (such as vincristine and methotrexate; see section 4.5).

Myelosuppression

Pegaspargase may cause myelosuppression, either directly or indirectly (by altering the myelosuppressive effects of other agents such as methotrexate or 6-mercaptopurine). Therefore, use of pegaspargase could increase the risk of infections.

The decrease in the number of circulating lymphoblasts is often quite marked, and normal or too low leukocyte counts are often seen in the first days after the start of therapy. This can be associated with a marked rise in the serum uric acid level. Uric acid nephropathy may develop. To monitor the therapeutic effect, the peripheral blood count and the patient's bone marrow should be monitored closely.

Hyperammonaemia

Asparaginase facilitates the rapid conversion of asparagine and glutamine to aspartic acid and glutamic acid, with ammonia as the shared by-product of both reactions (see section 5.1).

Intravenous administration of asparaginase may therefore cause serum levels of ammonia to rise sharply following administration.

The symptoms of hyperammonaemia are often transient in nature and can include: nausea, vomiting, headache, dizziness and rash. In severe cases, encephalopathy can develop with or without hepatic impairment, especially in older adults, which can be life-threatening or fatal. If symptoms of hyperammonaemia exist, ammonia levels should be monitored closely.

Contraception

Effective non-oral method of contraception must be used during pegaspargase treatment and for at least 6 months after pegaspargase discontinuation. Since an indirect interaction between the oral contraceptives and pegaspargase cannot be ruled out, the use of oral contraception is not considered an acceptable method of contraception (see sections 4.5 and 4.6).

Sodium content

This medicinal product contains less than 1 mmol sodium (23 milligram) per dose, that is to say essentially 'sodium-free'.

4.5. Interaction with other medicinal products and other forms of interaction

The decrease in serum proteins caused by pegaspargase can increase the toxicity of other medicinal products that are protein bound.

In addition, by inhibiting protein synthesis and cell division, pegaspargase can disturb the mechanism of action of other substances which require cell division for their effect, e.g. methotrexate.

Methotrexate and cytarabine can interfere differently with pegaspargase: their prior administration can increase the action of pegaspargase synergistically. If these substances are given subsequently, the effect of pegaspargase can be weakened antagonistically.

Pegaspargase can interfere with metabolism and clearance of other medicinal products, based on its effects on protein synthesis and hepatic function, as well as from its combined use with other chemotherapy products known to interact with CYP enzymes.

The use of pegaspargase can lead to fluctuation in coagulation factors. This can promote the tendency to bleeding and/or thrombosis. Caution is therefore needed when anticoagulants such as coumarin, heparin, dipyridamole, acetylsalicylic acid or nonsteroidal anti-inflammatory medicinal products are given concomitantly, or when concomitant chemotherapy regimen including methotrexate, daunorubicin, corticosteroids is administered.

When glucocorticoids (e.g. prednisone) and pegaspargase are given at the same time, alterations in coagulation parameters (e.g. fall in fibrinogen and Antithrombin III deficiency, ATIII) can be more pronounced.

Pegaspargase may increase the risk of glucocorticoid-induced osteonecrosis in children and adolescents when both treatments are given simultaneously, with a higher incidence seen in girls, through a potential increase in exposure of dexamethasone (see sections 4.4 and 4.8).

Immediately preceding or simultaneous treatment with vincristine can increase the toxicity of pegaspargase. Administration of pegaspargase before vincristine may increase the neurotoxicity of vincristine. Therefore, vincristine should be given at least 12 hours prior to administration of pegaspargase in order to minimise toxicity.

An indirect interaction cannot be ruled out between pegaspargase and oral contraceptives due to pegaspargase hepatotoxicity that may impair the hepatic clearance of oral contraceptives. Therefore, the concomitant use of pegaspargase with oral contraceptives is not recommended. Another method than oral contraception shoud be used in women of childbearing potential (see sections 4.4 and 4.6).

Simultaneous vaccination with live vaccines increases the risk of severe infections attributable to the immunosuppressive activity of pegaspargase, the presence of the underlying disease and combination chemotherapy (see section 4.4). Vaccination with live vaccines should therefore be given no earlier than 3 months after termination of the entire antileukaemic treatment.

4.6. Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Men and women should use effective contraception during treatment and for at least 6 months after pegaspargase discontinuation. Since an indirect interaction between oral contraceptives and pegaspargase cannot be ruled out, oral contraceptives are not considered sufficiently safe in such clinical situation. A method other than oral contraception should be used in women of childbearing potential (see sections 4.4 and 4.5).

Pregnancy

There are limited data on the use of L-asparaginase and no data on the use of pegaspargase in pregnant women. No reproduction studies in animals with pegaspargase were performed but studies in animals with L-asparaginase have shown teratogenicity (see section 5.3). Therefore and due to its pharmacological properties, pegaspargase should not be used during pregnancy unless the clinical conditions of the woman require treatment with pegaspargase.

Breast-feeding

It is not known whether pegaspargase is excreted in breast milk. Based on its pharmacological properties any risk to the breast-fed newborns/infants cannot be excluded. As a precautionary measure, breast-feeding should be discontinued during treatment with pegaspargase and should not be restarted until after discontinuation of pegaspargase.

Fertility

No studies investigating the effect of pegaspargase on fertility have been performed.

4.7. Effects on ability to drive and use machines

Pegaspargase has a major influence on the ability to drive and use machines. The following adverse reactions have been reported in patients treated with pegaspargase along with other chemotherapy medicinal products: somnolence, confusion, dizziness, syncope, seizure Patients should be advised not to drive or operate machines while receiving pegaspargase if they experience these or other adverse reactions which can impair their ability to drive or operate machines (see section 4.4).

4.8. Undesirable effects

a. Summary of the safety profile

The adverse reactions described in this section are derived from clinical studies data and post- marketing experience of pegaspargase in ALL patients. The safety profile is based on randomised, controlled, prospective, open-label multicentre studies using pegaspargase at a dose of 2500 U/m^2 administered intravenously as a comparative treatment (studies DFCI 11- 001 and AALL07P4. In addition, pegaspargase studies using the intramuscular route of administration (studies CCG-1962 and CCG-1991) were also considered to determine the safety profile (see section 5.1).

The most common adverse reactions with pegaspargase (observed in at least 2 studies with a frequency of >10%) included: alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, activated partial thromboplastin time prolonged, hypertriglyceridaemia,

hyperglycaemia, and febrile neutropenia.

The most common, severe adverse reactions with pegaspargase (graded 3 or 4) observed in studies DFCI 11-001 and AALL07P4 with a frequency of >5% included: alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, febrile neutropenia, hyperglycaemia, lipase increased, and pancreatitis.

b. Tabulated list of adverse reactions

Adverse reactions and their frequencies are reported in table 1. Frequencies are defined by 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), and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions reported with pegaspargase therapy

MedDRA Standard System Organ Class	**Adverse reaction**
Infections and infestations	
Common	Infections, sepsis
Blood and lymphatic system disorders	
Very common:	Febrile neutropenia
Common	Anaemia, coagulopathy
Not known:	Bone marrow failure
Immune system disorders	
Very common	Hypersensitivity, Urticaria, Anaphylactic reactions
Not known:	Anaphylactic shock
Metabolism and nutrition disorders	
Very common	Decreased appetite, hyperglycaemia
Common	hypercholesterolaemia, Hyperlipidaemia
Not known	Diabetic ketoacidosis, hypoglycaemia
Psychiatric disorders	
Not known	Confusional state
Nervous system disorders	
Common	Seizure, Peripheral Motor Neuropathy, Syncope
Rare	Posterior reversible leukoencephalopathy syndrome
Not known	Somnolence, tremor*
Vascular disorders	
Very common	Embolism**
Common	Thrombosis***
Not known	Cerebrovascular accident, haemorrhage, superior sagittal sinus thrombosis
Respiratory, thoracic and mediastinal disorders	
Common	hypoxia
Gastrointestinal disorders	
Very common	Pancreatitis, Diarrhoea, Abdominal pain, nausea
Common	Vomiting, stomatitis, ascites
Rare	Pancreatitis necrotising, pancreatitis haemorrhagic
Not known	Pancreatic pseudocyst, parotitis*

Hepatobiliary disorders	
Common	Hepatotoxicity, fatty liver
Rare	Hepatic necrosis, jaundice, cholestasis, hepatic failure
Not known	Veno-occlusive disease
Skin and subcutaneous tissue disorders	
Very common	Rash
Not known	Toxic epidermal necrolysis*
Musculoskeletal and connective tissue disorders	
Common	Pain in extremities
Not known	Osteonecrosis (see sections 4.4 and 4.5)
Renal and urinary disorders	
Not known	Renal failure acute*
General disorders and administration site conditions	
Not known	Pyrexia
Investigations	
Very common	Weight decreased, hypoalbuminaemia, alanine aminotransferase increased, aspartate aminotransferase increased, hypertriglyceridaemia, blood fibrinogen decreased, lipase increased, amylase increased, activated partial thromboplastin time prolonged, blood bilirubin increased, antithrombin III decreased****, neutrophil count decreased****
Common	Prothrombin time prolonged. international normalised ratio increased, hypokalaemia, blood cholesterol increased, hypofibrinogenaemia, gamma-glutamyl transferase increased
Not known	Blood urea increased, anti-pegaspargase antibodies, neutrophil count decreased, platelet count decreased, hyperammonaemia
*Adverse reactions observed with other asparaginases in the class **Cases of pulmonary embolism, venous thrombosis, venous thrombosis limb, and thrombophlebitis superficial were observed in DFCI 11-001 ***Legend: CNS thrombosis **** Cases of antithrombin III and neutrophil count decreased were observed in CL2- 95014-002 and CL2-95014-003	

c. Description of selected adverse reactions

The following adverse reactions have been observed in association with asparaginase therapy. Although they have not been specifically associated with the use of pegaspargase, they may occur with the use of pegaspargase:

Blood and lymphatic system disorders

Pegaspargase can cause mild to moderate myelosuppression, and all three blood cell lines can be affected. About half of all serious haemorrhages and thromboses affect cerebral vessels and can lead to e.g. stroke, seizure, headache or loss of consciousness.

Nervous system disorders

Pegaspargase may cause central nervous system dysfunctions manifesting as convulsions, and less frequently confusional state and somnolence (mildly impaired consciousness).

In rare cases, a reversible posterior leukoencephalopathy syndrome (RPLS) may occur. In very rare cases, mild tremor in the fingers has been described.

Gastrointestinal disorders

About half of patients develop mild to moderate gastrointestinal reactions such as loss of appetite, nausea, vomiting, abdominal cramps, diarrhoea and weight loss.

Acute pancreatitis can occur commonly. There have been isolated reports of formation of pseudocysts (up to four months after the last treatment).

Haemorrhagic or necrotising pancreatitis occurs rarely. One case of pancreatitis with simultaneous acute parotitis has been described with L-asparaginase treatment. In single cases, haemorrhagic or necrotising pancreatitis with fatal outcome has been reported.

Serum amylase can rise during and after the conclusion of pegaspargase therapy.

Renal and urinary disorders

Acute renal failure may develop in rare cases during treatment with

L-asparaginase-containing regimens.

Skin and subcutaneous tissue disorders

Allergic reactions can manifest on the skin. One case of toxic epidermal necrolysis (Lyell‘s syndrome) has been described in association with L-asparaginase.

Endocrine disorders

Alterations in endocrine pancreatic function are observed commonly and are expressed mainly in the form of abnormal glucose metabolism. Both diabetic ketoacidosis and hyperosmolar hyperglycaemia have been described, which generally respond to administration of insulin.

Metabolism and nutrition disorders

An alteration in serum lipid levels was observed and changes in serum lipid values, in most cases without clinical symptoms, are very common.

A rise in serum urea occurs regularly, is dose-independent and nearly always a sign of pre-renal metabolic imbalance.

General disorders and administration side conditions

Pyrexia can occur after the injection, which usually subsides spontaneously.

Immune system disorders

Specific antibodies to pegaspargase have been detected; uncommonly they were associated with hypersensitivity reactions. Neutralising antibodies reducing clinical efficacy were also recorded.

Hypersensitivity reactions to pegaspargase, including life-threatening anaphylaxis, angioedema, lip swelling, eye swelling, erythema, blood pressure decreased, bronchospasm, dyspnoea, pruritus and rash, can occur during therapy (see sections 4.3 and 4.4).

Hepatobiliary disorders

Alteration of liver parameters is common. A dose-independent rise in serum transaminases, and serum bilirubin is commonly observed.

A rapid weight gain, fluid retention with ascites, hepatomegaly, associated with rapid increase of serum bilirubin and persistent thrombocytopenia might indicate a risk of developing a severe VOD, which if left untreated, can be fatal (see section 4.4).

Fatty liver can be observed very frequently. There have been rare reports of cholestasis, icterus, hepatic cell necrosis and hepatic failure with fatal outcome.

Impaired protein synthesis can lead to a decline in the serum proteins. There is a dose- independent decrease in serum albumin in the majority of patients during the treatment.

The type of adverse reactions with pegaspargase are similar to those observed with native non- pegylated L-asparaginase (e.g. native *E. coli* asparaginase).

Reporting of suspected adverse reactions

Healthcare professionals are requested to report any suspected adverse reactions to the National Regulatory Authority.

Reporting of suspected adverse reactions:

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org.

4.9. Overdose

Cases of accidental overdose have been reported with pegaspargase. Following overdose, increased liver enzymes, rash and hyperbilirubinaemia have been observed.

There is no specific pharmacological treatment for the overdose. In case of overdose, patients must be carefully monitored for signs and symptoms of adverse reactions, and appropriately managed with symptomatic and supportive treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic groups: Antineoplastic and immunomodulating agents, other antineoplastic agents, ATC code: L01XX24

Mechanism of action

The mechanism of action of L-asparaginase is the enzymatic cleavage of the amino acid L- asparagine into aspartic acid and ammonia. Depletion of L-asparagine in blood results in inhibition of protein-synthesis, DNA-synthesis and RNA-synthesis, especially in leukaemic blasts which are not able to synthetise L-asparagine, thus undergoing apoptosis.

Normal cells, in contrast, are capable of synthesising L-asparagine and are less affected by its rapid depletion during treatment with the enzyme L-asparaginase. The PEGylation does not change the enzymatic properties of L-asparaginase, but it influences the pharmacokinetics and immunogenicity of the enzyme.

Pharmacodynamic effects

Anti-leukaemic effect of L-asparaginase is related to a sustained L-asparagine depletion in blood and cerebrospinal fluid (CSF). The pharmacodynamic (PD) effect of pegaspargase was assessed after intramuscular (Study CCG-1962) and intravenous administration (AALL07P4).

In Study CCG-1962, PD effect of pegaspargase was assessed through serial measurements of asparagine in serum (n=57) and CSF (n=50) of newly diagnosed paediatric patients with standard-risk ALL who received three intramuscular doses of pegaspargase (2500 Units/m^2 BSA), one each during induction of two during delayed intensification treatment phases. A reduction in serum asparagine concentration was evident by the 4th day after the first Induction dose and reached an apparent nadir by the 10th day after the dose. Serum asparagine concentrations of approximately 1µM persisted for approximately 3 weeks.

Asparagine concentration fell to <3 µM when asparginase activity was >0.1 U/mL. CSF asparagine of 2.3µM pre-treatment fell to 1.1 µ M on Day 7 and 0.6 µ M on Day 28 of Induction (see Clinical efficacy and safety).

In Study AALL07P4, the PD effect of pegaspargase was assessed in 47 evaluable subjects with high risk B-precursor ALL who received intravenous doses of pegaspargase 2,500 U/m^2 BSA during the Induction and Consolidation phases. Plasma L-asparagine concentrations were depleted to below the assay limit of quantification within 24 hours following the Induction and first Consolidation dose of pegaspargase and depletion was sustained for approximately two weeks. CSF asparagine concentrations were reduced by the 4th day following the Induction dose, and remained largely undetectable by the 18th day after dosing.

Based on results from these two studies, a 2,500 U/m^2 BSA dose of pegaspargase administered intramuscular (study 1CCG-1962) and intravenous (AALL07P4) provides maintenance of L-asparagine depletion for approximately two weeks following dosing.

Clinical efficacy and safety

Pegaspargase efficacy and safety were evaluated on the basis of three clinical studies using pegaspargase solution for injection/infusion in the first line treatment of ALL: Study CCG-1962 in standard risk ALL patients; Study AALL07P4 in high risk ALL patients; Study DFCI 11- 001 enrolled both standard and high-risk ALL patients.

Pegaspargase efficacy in ALL in patients with relapse/refractory disease and a history of prior clinical allergic reaction to native *E. coli* L-asparaginase was based on a pool of 94 patients from six open-label studies [ASP-001, ASP-201A, ASP-302, ASP-304, ASP-400 and ASP- 001C/003C].

First-Line (ALL patients non-hypersensitive to native E. coli L-asparaginase)

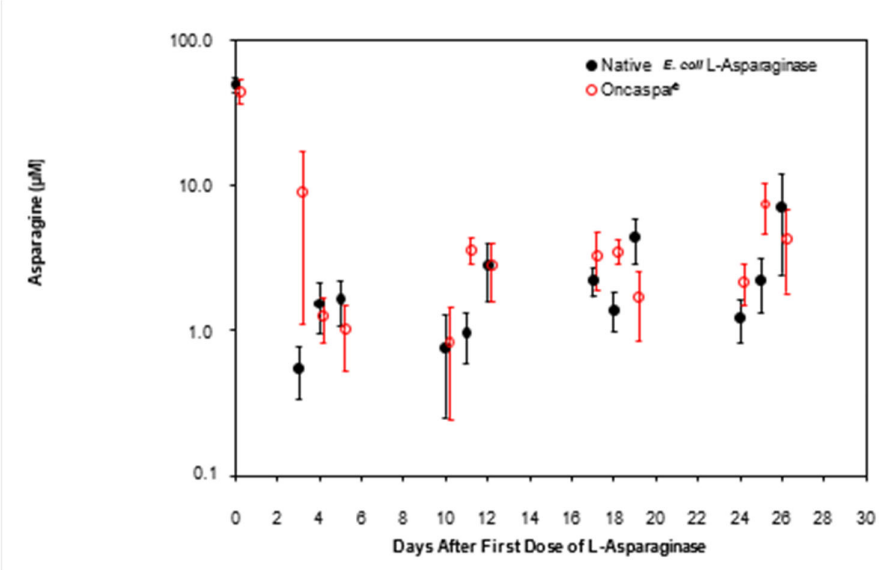
The safety and efficacy of pegaspargase was evaluated in an open-label, multicenter, randomized, active-controlled study (Study CCG-1962). In this study, 118 paediatric patients aged 1 to 9 years with previously untreated standard-risk ALL were randomized 1:1 to pegaspargase or native *E. coli* L-asparaginase as part of combination therapy. Pegaspargase was administered intramuscularly at a dose of 2500 Units/m^2 BSA on Day 3 of the 4-week Induction phase and on Day 3 of each of two 8-week Delayed Intensification (DI) phases. Native *E. coli* L-asparaginase was administered intramuscularly at a dose of 6,000 Units/m^2 BSA three times weekly for a total of 9 doses during induction and for a total of 6 doses during each delayed intensification

phase.

The primary determination of efficacy was based on demonstration of similar asparagine depletion (magnitude and duration) in the pegaspargase and native *E. coli* L-asparaginase arms. The protocol-specified goal was achievement of asparagine depletion to a serum concentration of ≤1 μM. The proportion of patients with this level of depletion was similar between the 2 study arms during all 3 phases of treatment at the protocol-specified time points.

In all phases of treatment, serum asparagine concentrations decreased within 4 days of the first dose of asparaginase in the treatment phase and remained low for approximately 3 weeks for both pegaspargase and native *E. coli* L-asparaginase arms. Serum asparagine concentrations during the Induction phase are shown in Figure 1. The patterns of serum asparagine depletion in the 2 delayed intensification phases are similar to the pattern of serum asparagine depletion in the induction phase.

Figure 1: Mean (± standard error) serum asparagine during Study 1 Induction phase



Note: Pegaspargase (2,500 Units/m^2 BSA intramuscular) was administered on Day 3 of the 4- week Induction phase. Native *E. coli* L-asparaginase (6,000 Units/m^2 BSA intramuscular) was administered 3 times weekly for 9 doses during Induction.

CSF asparagine concentrations were determined in 50 patients during the induction phase. CSF asparagine decreased from a mean pre-treatment concentration of 3.1 µM to 1.7 µM on Day 4 ± 1 and 1.5 µM at 25 ± 1 days after administration of pegaspargase. These findings were similar to those observed in the native *E. coli* L-asparaginase treatment arm.

Event-Free Survival (EFS) for the pegaspargase and native *E. coli* L-asparaginase arms are summarized in Table 2, Study CCG-1962 was not designed to evaluate for differences in EFS rates.

Table 2: Event-free survival rate at 3, 5 and 7 years (Study CCG-1962)

	Pegaspargase	**native *E. coli* L-asparaginase**
3-Year EFS Rate, % (95% CI)	83 (73, 93)	79 (68, 90)
5-Year EFS Rate, % (95% CI)	78 (67, 88)	73 (61, 85)
7-Year EFS Rate, % (95% CI)	75 (63, 87)	66 (52, 80)

In Study CCG-1962, the most common adverse reactions were infections, including two life- threatening infections (1 patient in each arm). In general, incidence and type of adverse reactions Grade 3 and 4 were similar between the two treatment groups. Two patients in the pegaspargase arm had allergic reactions during Delayed Intensification (DI) DI #1 (Grade 1 allergic reaction and Grade 3 hives).

A pilot study was conducted for newly diagnosed patients from 1 to <31 years of age with high risk B-precursor ALL (Study AALL07P4). This was an open-label, controlled, randomized study comparing an investigational pegylated asparaginase product to pegaspargase as a component of multi-agent chemotherapy in the first line treatment of ALL. White blood cell (WBC) criteria were: a) Age 1-10 years: WBC ≥ 50,000/μL; b) Age 10-30 years: Any WBC;

c) Prior steroid therapy: Any WBC. Patients were not allowed prior cytotoxic chemotherapy with the exception of steroids and intrathecal cytarabine. A total of 166 patients were enrolled in this study; 54 patients were randomized to treatment with 2500 U/m^2 BSA pegaspargase and

111 patients were randomized to the investigational pegylated asparaginase product. Pegaspargase was administered intravenously at the dose of 2500 Units/m^2 BSA during Induction, Consolidation, Delayed Intensification, and Interim Maintenance phases in patients with high-risk ALL receiving augmented Berlin-Frankfurt-Munster therapy.

The percentage of patients in the pegaspargase treatment arm with evaluable minimal residual disease (MRD) negative status (<0.1% leukaemia cells in bone marrow) at Day 29 of Induction was 80% (40/50). At 4-years, the EFS and overall survival (OS) for the pegaspargase treatment arm were 81.8% [95% CI 62.9-91.7%] and 90.4% [95% CI 78.5-95.9%], respectively. Overall, in the group receiving pegaspargase, the rate of all grade hypersensitivity was 5.8%, anaphylactic reactions was 19.2%, and pancreatitis 7.7%. Grade 3 or higher febrile neutropenia was 15.4%.

Study DFCI 11-001, conducted by the Dana-Farber Cancer Institute (DFCI), is an ongoing, active-controlled, randomised multicentre study of an intravenous investigational pegylated asparaginase product versus pegaspargase, in children and adolescents aged 1 to <22 years with newly diagnosed ALL treated with a DFCI ALL consortium therapeutic backbone. A total of 239 patients were randomised, 237 of whom were treated with study drug (146 male and 91 female), of these, 119 patients (115 with a diagnosis of ALL) were treated with pegaspargase 2500 U/m^2. Treatment was administered during Induction (Day 7), and then every 2 weeks for a total of 30 weeks post-Induction therapy. Randomisation of patients was stratified based on risk group (standard/high/very high risk), including both B- and T-cell ALL. The percentage of patients in the pegaspargase arm with evaluable Low End-Induction MRD (<0.001 detectable disease) at Day 32 was 87.9% (80/91). The One-year EFS was 98.0 [95%CI 92.3, 99.5]; the
One-year OS was 100 [95% CI 100, 100] in this study.

ALL patients hypersensitive to native E. coli L-asparaginase

Six open-label studies evaluated pegaspargase in relapse/refractory haematological diseases. In these studies, a total of 94 patients with ALL diagnosis with a history of prior clinical allergic reaction to native *E. coli* L-asparaginase were exposed to pegaspargase. One patient received pegaspargase doses of 250 and 500 Units/m^2 BSA intravenously. The remaining patients were treated with 2000 or 2500 U/m^2 BSA administered intramuscularly or intravenously. Patients received pegaspargase as a single agent or in combination with multi-agent chemotherapy. Overall, from five studies analysed based on 65 ALL patients exposed to pegaspargase using the highest therapeutic response during the entire study, complete remission were observed in 30 patients (46%), partial remission in 7 patients (11%) and haematological improvement in 1 patient (2%). In the other study, with 29 hypersensitive ALL patients exposed to pegaspargase,

11 patients were evaluated for response during induction. Of these, 3 patients achieved complete remission (27%), 1 patient had partial remission (9%), 1 patient had haematologic improvement (9%) and 2 patients had therapeutic efficacy (18%). Therapeutic efficacy was defined as a clinical improvement which did not meet the criteria for other beneficial outcomes. During the maintenance phase, 19 patients were evaluated, with 17 patients achieving complete remission (89%), and 1 patient (5%) with therapeutic efficacy.

5.2. Pharmacokinetic properties

Pegaspargase pharmacokinetic properties were based on asparaginase activity measured by an enzymatic assay after intramuscular (CCG-1962) and intravenous (AALL07P4, DFCI 11-001) administration.

In Study CCG-1962, mean asparaginase activity reached peak value of 1 U/mL on Day 5 after the injection. The mean half-life after absorption from the injection site was 1.7 days and the elimination half-life was 5.5 days. The volume of distribution at steady-state and clearance were estimated at 1.86 L/m^2 and 0.169 L/m^2 per day, respectively.

In Study AALL07P4, PK parameters after a single 2,500 U/m^2 intravenous dose during Induction were calculated by noncompartmental PK analysis from sequential plasma samples and are depicted in Table 3 (see section 5.1). The Cmax and AUC of pegaspargase trended lower in males, subjects with larger BMI, and subjects >10 years. During Induction, following a single intravenous dose of pegaspargase 2,500 U/m^2, asparaginase activity ≥ 0.1 U/mL was sustained for up to 18 days post-dose in 95.3% of subjects.

Table 3: Pharmacokinetic Parameters After a Single

intravenous Dose of pegaspargase 2,500 U/m2 BSA During Induction (N=47; Study 2)

PK Parameters	Arithmetic Mean (SD)
C_{max} (mU/mL)*	1638 (459.1)
T_{max} (hr)*	1.25 (1.08, 5.33)†
AUC_{0-t} (mU· day/mL)*	14810 (3555)
$AUC_{0-\infty}$ (mU· day/mL)‡	16570 (4810)
$t_{1/2}$ (day)‡	5.33 (2.33)
CL (L/day)‡	0.2152 (0.1214)
Vss (L)‡	1.95 (1.13)

* N=47 evaluable subjects.
† Median (10^{th}, 90^{th} percentiles).
‡ N= 46 evaluable subjects.

In Study DFCI 11-001, assessments of asparaginase activity were performed following a single intravenous dose of pegaspargase 2,500 U/m^2 BSA during Induction, and every two weeks during post-Induction (see section 5.1). During Induction, plasma asparaginase activity ≥ 0.1 U/mL was sustained in 93.5% of subjects 18 days after administration. During the post-Induction phase, a nadir (trough) asparaginase activity above 0.4 U/mL was sustained in 100% of subjects from Week 7 up until Week 25. These results indicate that, when pegaspargase 2,500 U/m^2 BSA is administered as single and repeated doses every two weeks, clinically relevant asparaginase activity is sustained over the entire dosing interval (i.e., two weeks).

Patients with newly diagnosed ALL received a single intramuscular injection of pegaspargase (2500 U/m² body surface area) or native asparaginase from *E. coli* (25000 U/m² body surface area) or from *Erwinia* (25000 U/m² body surface area). The plasma elimination half-life of pegaspargase was statistically significantly longer (5.7 days) than the plasma elimination half- lives of the native asparaginases from *E. coli* (1.3 days) and *Erwinia* (0.65 days). The immediate cell death of leukaemic cells *in vivo*, measured by rhodamine fluorescence, was the same for all three L-asparaginase preparations.

ALL patients with several relapses were treated either with pegasparagse or with native asparaginase from *E. coli* as part of an induction therapy. Pegasparagse was given in a dose of 2500 U/m² body surface intramuscularly on days 1 and 15 of induction. The mean plasma half- life of pegasparagse was 8 days in non- hypersensitive patients (AUC 10.35 U/ml/day), and 2.7 days in hypersensitive patients (AUC 3.52 U/ml/day).

Specific populations

The controlled studies were not designed to formally evaluate the pharmacokinetics of pegaspargase in specific populations. A population pharmacokinetic evaluation of pegaspargase based on data obtained from Studies AALL07P4 (IV), DFCI 11-001 (IV), and Study CCG-1962 (IM) identified that clearance (linear and saturable) increased approximately proportionally to BSA and volume of distribution increased slightly more proportionally to BSA. No statistically significant differences in PK characteristics between male and female subjects were identified in this analysis.

The impact of renal and hepatic impairment on the PK of pegaspargase has not been evaluated. As pegaspargase is a protein with a high molecular weight, it is not excreted renally,

and no change of pharmacokinetic of pegaspargase in patients with renal impairment is foreseen.

Since the proteolytic enzymes responsible for pegaspargase metabolism are ubiquitously distributed in tissues the exact role of the liver is unknown: however any decrease in liver function is not expected to present clinical relevant problems in the use of pegaspargase.

There are no data available for elderly patients

5.3. Preclinical

safety data Toxicity

Study

a) Acute Intravenous Toxicity Study in Swiss Albino Mouse:

The study now reported was designed to determine the acute intravenous toxicity of pegaspargase to the Swiss Albino mice. No signs of toxicity were observed in animals treated with different doses of pegaspargase via intravenous route. All animals survived through the

study period of 14 days. Gross pathological examination did not reveal any abnormalities attributable to the treatment.

It was concluded that the acute lethal intravenous dose of pegaspargase in Swiss Albino mice was found to be greater than 10000 IU/kg body weight.

b) Acute Intravenous Toxicity Study in Sprague Dawley Rat:

The study now reported was designed to determine the acute intravenous toxicity of pegaspargase to the Sprague Dawley rats. No signs of toxicity were observed in animals treated with different doses of pegaspargase via intravenous route. All animals survived through the study period of 14 days. Gross pathological examination did not reveal any abnormalities attributable to the treatment.

It was concluded that the acute lethal intravenous dose of pegaspargase in Sprague Dawley rats was found to be greater than 10000 IU/kg body weight.

c) Subchronic intra venous toxicity study in the Swiss Albino Mouse

The Subchronic intravenous toxicity study was designed and conducted to determine the toxicity profile of pegaspargase when administered by intravenous route daily for 28 days to Swiss Albino mice.

Pegaspargase diluted with water for injection was administered to mice via intravenous route at the dose levels ranging from 0 IU/kg to 3200 IU/kg i.e. 0 IU/kg, 800 IU/kg, 1600 IU/kg and 3200 IU/kg body weight.

d) Subchronic intra venous toxicity study in the Sprague Dawley Rat

The subchronic intravenous toxicity study was designed and conducted to determine the toxicity profile of pegaspargase when administered daily for 28 days to Sprague Dawley rats.

Pegaspargase diluted with water for injection was administered to rats via intravenous route at the dose levels ranging from 0 IU/kg to 400 IU/kg i.e. 0 IU/kg, 100 IU/kg, 200 IU/kg and 400 IU/kg body weight. Salient features of the study were as follows:

1. Male and female animals from control and different dose groups survived through the dosing period of 28 days.
2. No signs of toxicity were observed in male and female animals from different dose groups during the dosing period of 28 days.
3. Reduced body weight gain of 12.16%, 16.59% and 17.99% was observed in male animals from 100 IU/kg, 200 IU/kg and 400 IU/kg dose groups when compared with controls at the end of the dosing period of 28 days. Reduced body weight gain of 8.20% and 10.21% was observed in female animals from 200 IU/kg and 400 IU/kg dose groups when compared with controls at the end of the dosing period of 28 days.
4. Reduced food intake was observed in male from 100 IU/kg, 200 IU/kg and 400 IU/kg dose groups and in female animals from 200 IU/kg and 400 IU/kg dose groups.
5. Haematological analysis revealed no abnormalities attributable to the treatment.
6. Biochemical analysis revealed no abnormalities attributable to the treatment.
7. Organ weight data of male animals revealed increased relative weights of brain of animals from 400 IU/kg dose group and decreased relative weights of spleen of animals from 100 IU/kg dose group.
8. Organ weight data of female animals revealed decreased relative weights of heart of animals from 400 IU/kg dose group.
9. Gross pathological examination did not reveal any

abnormality attributable to the treatment.

10. Histopathological examination revealed minimal to mild vacuolation of liver in one male and one female animal from 400 IU/kg dose group.
11. Based on these findings, it is concluded that p**egaspargase** when administered to Sprague Dawley rats via intravenous route, over a period of 28 days as expected resulted in significantly reduced body weight gain, feed intake at all dose levels studied and histological changes in male and female animals from 400 IU/kg body weight. The No Observed Adverse Effect Level (NOAEL) was found to be less than 100 IU/kg body weight in male and female animals.

Immunogenicity

No immunogenic response was detected in a 12-week study in mice in which pegaspargase was administered weekly at the dose of 10.5 U/mouse intramuscularly or intraperitoneally.

Reproductive toxicity

No studies of reproductive toxicity were conducted with pegaspargase.

Embryotoxicity studies with L-asparaginase have showed evidence of teratogenic potential in rats treated from day 6 to 15 of gestation with a No Observed Effect Level (NOEL) for teratogenic effects at 300 U/kg intravenously. In rabbits doses of 50 or 100 U/kg intravenous on days 8 and 9 of gestation induced viable foetuses with congenital malformations: no NOEL has been determined. Multiple malformations and embryolethal effects were observed with doses in the therapeutic range. Investigations of the effect on fertility and peri- and postnatal development were not conducted.

Carcinogenicity, mutagenicity, fertility

Long-term investigations of carcinogenicity or studies of the effect on fertility in animals were not conducted with pegaspargase.

Pegaspargase was not mutagenic in the Ames test using *Salmonella typhimurium* strains.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Dibasic sodium phosphate

Monobasic sodium phosphate

Sodium chloride

Water for injections

6.2. Incompatibilities

None known so far.

6.3. Shelf life

24 months from the date of manufacturing, when stored as described below.

6.4. Special precautions for storage

The product should be stored at 2°C to 8°C and protected from light. Do not freeze or shake. Single use vials

6.5. Nature and contents of container

5 mL Single Use Vial

Clear Type I 750 IU per mL

Pegaspargase Injection is filled in USP Type I Glass vial. One such labelled vial is placed in a Plastic Tray and which is packed in Monocarton along with leaflet.

6.6. Special precautions for disposal and other handling Administration

1. Parenteral medicinal products should be inspected for particulate matter prior to administration, only a clear, colourless solution free from visible foreign particles should be used.
2. The medicinal product should be administered intravenously or intramuscularly. The solution should be administered slowly.

   For intramuscular injection, the volume should not exceed 2 ml in children and adolescents and 3 ml in adults.

   For intravenous administration, the reconstituted solution should be diluted in 100 ml sodium chloride 9 milligram per mL (0.9%) solution for injection or 5% glucose solution.

   The diluted solution can be given over 1 to 2 hours together with an already-running infusion of either sodium chloride 9 milligram per ml or 5% glucose. Do not infuse other medicinal products through the same intravenous line during administration of pegaspargase (see section 4.2).

Disposal

Pegaspargase is for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Gennova Biopharmaceuticals Limited

Block 1, Plot No: P-1 & P-2, ITBT Park,

Phase-II, MIDC Hinjawadi, Pune-411 057,

Maharashtra, INDIA

8. MARKETING AUTHORISATION NUMBER(S)

CTD12586/26468

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05-11-2025

10. DATE OF REVISION OF THE TEXT

05-11-2025

Package leaflet: Information for the user HAMSYL®
(Pegaspargase Injection 3750 IU/5 mL)

Read all of this leaflet carefully before you use/are given this medicine because it containsimportant information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet.

See section 4.

What is in this leaflet

a) WHAT IS HAMSYL AND WHAT IT IS USED FOR

Hamsyl contains pegaspargase, a pegylated form of the enzyme L-asparaginase, that breaks down asparagine, an important building block of proteins without which cells cannot survive. Normal cells can makeasparagine for themselves, while some cancer cells cannot. Hamsyl depletes the asparagine level in blood cancer cells, leading to selective cancer cell death.

Hamsyl is used to treat acute lymphoblastic leukaemia (ALL) in children from birth to 18 yearsand adults, and especially in patients allergic to native asparaginase. ALL is a white blood cell cancer type in which certain immature white cells (named lymphoblasts) start

growing out of control thus preventing the production of functional blood cells. Hamsyl is also used together with other medicines.

b) **BEFORE USING HAMSYL**

Do not use Hamsyl:

- if you are allergic to pegaspargase or to any of the other ingredients of this medicine (listed in section 6).
- If you have severe hepatic disease
- if you ever had pancreatitis.
- if you ever had severe bleeding following asparaginase therapy.
- if you ever had blood clots following asparaginase therapy.

Tell your doctor if any of these conditions apply to you. If you are the parent of a child who isbeing treated with Hamsyl, please tell the doctor if any of them apply to yourchild.

Warnings and precautions Do not take Hamsyl

Talk to your doctor before you are given Hamsyl. This medicine may not be suitable for you:

- if you have had serious allergic reactions to other forms of asparaginase, for example, difficulty in breathing,

flushing or swelling of the airways, or itching.

- if you suffer from a bleeding disorder or have had serious blood clots.
- if you get a fever.
- if you experience severe abdominal pain, which may be indicative of pancreatitis. In this case the pegaspargase
- therapy should be discontinued. If pancreatitis is confirmed, pegaspargase should not be restarted.
- if you have had poor liver function or are using other medicines which may harm the liver. Combination therapy with pegaspargase product and other hepatotoxic products can result in severe hepatic toxicity, hence caution is required, especially if there is pre-existing hepatic impairment.

This medicine can lead to fluctuations in clotting factors and may increase the risk of bleeding and/or clotting.

A side effect called osteonecrosis (bone damage) has been reported in the post-marketing setting in children and adolescents receiving pegaspargase (higher incidence seen in girls), especially when taken concomitantly with glucocorticoids (e.g. dexamethasone).

If you are the parent of a child being treated with Hamsyl, tell the doctor if any of the above conditions apply to your child.

During treatment with Hamsyl

During Hamsyl administration you will be closely watched for an hour after the start of treatment for any signs of serious allergic reactions. Medical equipment to treat allergic reactions will be available nearby.

<u>Additional monitoring tests</u>

Blood and urine, sugar levels, liver and pancreatic function and other tests will be carried out regularly to monitor your health during and after treatment because this medicine can affect blood and other organs.

Other medicines and Hamsyl

Tell your doctor if you are using/or have recently used or might use any other medicines. This is important as Hamsyl may increase the side effects of other medicines through its effect on theliver which

plays an important role in removing medicines from the body. In addition, it is especially important to tell your doctor if you are also using any of the following medicines:

- immunization with live vaccines within three months of completing your leukaemia treatment. This will increase the risk of severe infections.
- vincristine, another cancer medicine, if used at the same time as pegaspargase leads to anincreased risk of side effects or allergic reactions.
- such as anticoagulants (e.g., coumarin/warfarin and heparin), dipyridamol, acetylsalicylic acid or non-steroidal anti-inflammatory medicines (such as ibuprofen or naproxen). If used at the same time as pegaspargase, there is a higher risk of bleeding disorders.
- which require cell division for their effect, for example, methotrexate (amedicine used for cancer as well as arthritis treatment) may have a decrease in its effect.
- prednisone, a steroid medicine. If used at the same time as pegaspargase, the effects on the clotting ability of your blood are increased.
- cytarabine, a medicine which can be used in cancer treatment, and could interfere with the effect of pegaspargase.

Pegaspargase can also cause changes in liver function which can affect the way other medicines work.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for

advice before using this medicine.

Pegaspargase can cause harm to the fetus when administered to a pregnant woman. You should not use pegaspargase if you are pregnant because its effects during pregnancy have not been studied. Women ofchildbearing potential must use reliable contraception during treatment, and for at least 6 months after last dose of Hamsyl treatment.

It is not known whether pegaspargase is excreted into the breast milk. As a precautionary measure, breast-feeding should be discontinued during treatment with Hamsyl and should not be re-started until after treatment with pegaspargase has been discontinued.

Driving and using machines

Do not drive or use machines when using this medicine because it may make you feel drowsy, tired or confused.

Hamsyl contains sodium

This medicine contains less than 1 mmol sodium per dose, that is to say essentially ´sodium-free´.

c) **HOW TO USE HAMSYL**

Before administration, you might receive combination of medicines to help reduce your chances of getting allergic reactions. Your doctor will decide whether such premedication is necessary.
Your treatment with Hamsyl should be prescribed by a doctor experienced in medicines used to treat cancer. Your doctor will decide what dose of the medicine is needed and how often, based on your age and body surface area which is calculated from your height and weight.

The medicine is given as a solution by injection into a muscle or, if more suitable, into avein (intramuscular or intravenous administration).

If you are given too much Hamsyl than you should

As your doctor will administer the medicine, it is very unlikely you will be given more than you need.

In the unlikely event of accidental overdose, you will be monitored carefully by medical staff for signs and symptoms of adverse reactions, and appropriately managed with symptomatic and supportive treatment.

If you have any further questions on the use of this medicine, ask your doctor.

d) POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Tell your doctor **immediately** if you get any of the following side effects:

Very common (may affect more than 1 in 10 people)

- Inflammation or other disorders of the pancreas (pancreatitis) causing severe stomach pain which may spread to your back, vomiting, increase in blood sugar levels;
- Serious allergic reactions with symptoms such as rash, itching, swelling, hives, shortnessof breath, fast heart beat and drop in blood pressure.
- Blood clots
- Fever with low counts of white blood cells

Common (may affect up to 1 in 10 people)

- Severe bleeding or bruising;
- Violent shaking (seizures) and loss of consciousness;
- Severe infection with very high fever;
- Problems with your liver (e.g., change in color of your skin or urine or stool and laboratory results of elevated liver enzymes or bilirubin).

Rare (may affect up to 1 in 1,000 people)

- Liver failure.
- Jaundice
- Blocked bile flow from the liver (cholestasis)
- Destruction of liver cells (liver cell necrosis)

Not known (frequency cannot be estimated from the available data)

- Severe skin reaction called toxic epidermal necrolysis;
- Loss of kidney function (e.g., change in urine output, swelling of feet and ankles);
- Stroke.
- Severe allergic reaction that may cause loss of consciousness and could be life-threatening (anaphylactic shock)
- Bone damage (osteonecrosis).

Other side effects

Talk to your doctor if you get any of the following:

Very common (may affect more than 1 in 10 people)

- Changes in the function of the pancreas
- Weight loss;
- Leg pain (which could be a symptom of thrombosis), chest pain or shortness of breath (which may be a symptom of blood clots in the lungs, called pulmonary embolism)
- Loss of appetite, general weakness, vomiting, diarrhoea, nausea
- Increased blood sugar levels

Common (may affect up to 1 in 10 people)

- Decreased number of red blood cells

- Build-up of fluid in the stomach (ascites)
- Fever and flu-like symptoms;
- Mouth sores;
- Back, joint or abdominal pain
- High levels of fat and cholesterol in your blood
- Low potassium in your blood

Rare (may affect up to 1 in 1,000 people)

- Reversible posterior leukoencephalopathy syndrome (RPLS), a syndrome characterised by headache, confusion, seizures and visual loss which resolves after some time.

Not known (frequency cannot be estimated from the available data)

- Decreased number of white blood cells and platelets
- fever
- cysts in your pancreas, swelling of the salivary glands
- high levels of urea in your blood; antibodies against pegaspargase; high levels of ammonia in your blood; decreased blood sugar levels;
- sleepiness, confusion, mild twitching of the fingers.

e) HOW TO STORE HAMSYL

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C-8°C). Do not freeze.

Do not use if you notice any particulate matter or any visible foreign particles in the solution.

Do not throw away any medicines via waste-water or household waste. Ask the pharmacist how to dispose of unused medicines. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. These measures will help protect the environment.

f) FURTHER INFORMATION

What Hamsyl contains

The active substance is pegaspargase (pegylated L-asparaginase). 5 ml of solution contains 3750 IU pegaspargase.

1 ml of solution contains 750 IU

pegaspargase (750 U/ml). The

other ingredients are:

Dibasic sodium phosphate, Monobasic sodium phosphate, Sodium chloride, Water for injections

What Hamsyl looks like and contents of the pack

5 mL Single use

USP Type I Vial 750

IU per mL

Marketing Authorization Holder and Manufacturer

Gennova Biopharmaceuticals Limited.
Block 1, Plot No: P-1 & P-2,
ITBT Park, Phase-II, MIDC
Hinjawadi, Pune-411 057,
Maharashtra, INDIA

Manufacturer

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Hinjawadi, Pune-411 057
Maharashtra, INDIA

To report any adverse event, please write to: Safety@gennova.co.in

This leaflet was last approved in (07/2025)