Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

NIPENT 10 mg powder for solution for injection, powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 10 mg Pentostatin.

When reconstituted (see Section 6.6), the resulting solution contains pentostatin 2 mg/mL.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection, powder for solution for infusion.
The vials contain a solid white to off-white cake or powder.
The pH of reconstituted solution is 7.0 – 8.2.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Pentostatin is indicated as single agent therapy in the treatment of adult patients with hairy cell leukaemia.

4.2 Posology and method of administration

Pentostatin is indicated for adult patients.

Administration to patient

It is recommended that patients receive hydration with 500 to 1,000 ml of 5% glucose only or 5% glucose in 0.18% or 0.9% saline or glucose 3.3% in 0.3% saline or 2.5% glucose in 0.45% saline or equivalent before pentostatin administration. An additional 500 ml of 5% glucose only or 5% glucose in 0.18% or 0.9% saline or 2.5% glucose in 0.45% saline or equivalent should be administered after pentostatin is given.

The recommended dosage of pentostatin for the treatment of hairy cell leukaemia is 4 mg/m^2 in a single administration every other week. Pentostatin may be given intravenously by bolus injection or diluted in a larger volume and given over 20 to 30 minutes. (See Special precautions for disposal and other handling under Section 6.6).

Higher doses are not recommended.

No extravasation injuries were reported in clinical studies.

The optimal duration of treatment has not been determined. In the absence of major toxicity and with observed continuing improvement, the patient should be treated until a complete response has been achieved. Although not established as required, the administration of two additional doses has been recommended following the achievement of a complete response.

All patients receiving pentostatin at 6 months should be assessed for response to treatment. If the patient has not achieved a complete or partial response, treatment with pentostatin should be discontinued.

If the patient has achieved a partial response, pentostatin treatment should be continued in an effort to achieve a complete response. At any time thereafter that a complete response is achieved, two additional doses of pentostatin are recommended. Pentostatin treatment should then be stopped. If the best response to treatment at the end of 12 months is a partial response, it is recommended that treatment with pentostatin be stopped.

Withholding or discontinuation of individual doses may be needed when severe adverse reactions occur. Drug treatment should be withheld in patients with severe rash, and withheld or discontinued in patients showing evidence of nervous system toxicity.

Pentostatin treatment should be withheld in patients with active infection occurring during the treatment but may be resumed when the infection is controlled.

Dosage in Patients with Cytopenias

No dosage reduction is recommended at the start of therapy with pentostatin in patients with anaemia, neutropenia, or thrombocytopenia. In addition, dosage reductions are not recommended during treatment in patients with anaemia and thrombocytopenia. Pentostatin should be temporarily withheld if the absolute neutrophil count during treatment falls below 200 cells/mm^3 in a patient who had an initial neutrophil count greater than 500 cells/mm^3 and may be resumed when the count returns to predose levels.

Renal Insufficiency

There is limited experience in patients with impaired renal function (creatinine clearance (Clcr) <60 ml/min) (see section 5.2). Creatinine clearance should be determined prior to each administration of NIPENT.

Liver Impairment

Because of limited experience treating patients with abnormal liver function, treatment of such patients should be done with caution.

Administration to Elderly Patients

The recommended dosage of pentostatin for the treatment of hairy cell leukaemia in the elderly is 4 mg/m^2 in a single administration every other week. Clinical trials have included patients over 65 years old and no adverse reactions specific to this age group have been reported.

Paediatric Use

Hairy cell leukaemia is a disease affecting adults, most commonly in the sixth decade of life. Safety and effectiveness of Nipent in children have not been established.

4.3 Contraindications

Pentostatin is contraindicated in patients who have demonstrated hypersensitivity to the active ingredient or to any of the excipients.

Pentostatin is contraindicated in patients with impaired renal function (Creatinine clearance < 60 ml/min).

Pentostatin is contraindicated in patients with active infection.

4.4 Special warnings and precautions for use

Warnings

Pentostatin should be administered under the supervision of a physician qualified and experienced in the use of cancer chemotherapeutic agents. The use of doses higher than those specified (see Section 4.2) is not recommended. Dose-limiting severe renal, liver, pulmonary, and CNS toxicities occurred in Phase 1 studies that used pentostatin at a higher dose (20-50 mg/m^2/course) than recommended.

In a clinical investigation in patients with refractory chronic lymphocytic leukaemia using pentostatin at the recommended dose in combination with fludarabine phosphate, four of six patients entered on the study had severe or fatal pulmonary toxicity. The use of pentostatin in combination with fludarabine phosphate is not recommended.

Biochemical studies have demonstrated that pentostatin enhances the effects of vidarabine, a purine nucleoside with antiviral activity. The combined use of vidarabine and pentostatin may result in an increase in adverse reactions associated with each drug. The therapeutic benefit of the drug combination has not been established.

Patients with hairy cell leukaemia may experience myelosuppression primarily during the first few courses of treatment. Patients with infections prior to pentostatin treatment have in some cases developed worsening of their condition leading to death; whereas others have achieved complete response. Patients with infection should be treated only when the potential benefit of treatment justifies the potential risk to the patient. Efforts should be made to control the infection before treatment is initiated or resumed.

In patients with progressive hairy cell leukaemia, the initial courses of pentostatin treatment were associated with worsening of neutropaenia. Therefore, frequent monitoring of complete blood counts during this time is necessary. If severe neutropenia continues beyond the initial cycles, patient should be evaluated for disease status, including a bone marrow examination.

Pentostatin might have harmful effects on the genotype. Therefore, it is recommended that men undergoing treatment with pentostatin should not father a child during treatment up to 3 months thereafter. Contraception is to be guaranteed for women of childbearing age during treatment and for at least 6 months following the last dose of pentostatin. Should a pregnancy occur during treatment, the possibility of a genetic consultation is to be considered (See Section 4.6, Fertility, pregnancy and lactation).

Bone Marrow Transplant Regimen with high dose cyclophosphamide

Acute pulmonary oedema and hypotension leading to death, have been reported in the literature in patients treated with pentostatin in combination with carmustine, etoposide and high dose cyclophosphamide as part of an ablative regimen for bone marrow transplant. The combination of pentostatin and high dose cyclophosphamide is not recommended. Elevations in liver function tests occurred during treatment with pentostatin and were generally reversible.

Renal toxicity was observed at higher doses in early studies; however, in patients treated at the recommended dose, elevations in serum creatinine were usually minor and reversible. There were some patients who began treatment with normal renal function who had evidence of mild to moderate toxicity at a final assessment. (See Administration to Patient [4.2].)

Rashes, occasionally severe, were commonly reported and may worsen with continued treatment. Withholding of treatment may be required. (See Administration to Patient [4.2].)

Extra care should be taken in treating patients beginning therapy with poor performance.

Precautions

Therapy with pentostatin requires regular patient observation and monitoring of haematologic parameters and blood chemistry values. If severe adverse reactions occur, the drug should be withheld (see Administration to Patient [4.2]) and appropriate corrective measures should be taken according to the clinical judgement of the physician.

Pentostatin treatment should be withheld or discontinued in patients showing evidence of nervous system toxicity.

Prior to initiating therapy with pentostatin, renal function should be assessed with a serum creatinine and/or a creatinine clearance assay. (See Pharmacokinetic Properties [5.2], Administration to Patient [4.2].) Complete blood counts, serum creatinine, and BUN should be performed before each dose of pentostatin and at appropriate periods during therapy. Severe neutropenia has been observed following the early courses of treatment with pentostatin and therefore frequent monitoring of complete blood counts is recommended during this time. If haematologic parameters do not improve with subsequent courses, patients should be evaluated for disease status, including a bone marrow examination. Periodic monitoring of the peripheral blood for hairy cells should be performed to assess the response to treatment.

In addition, bone marrow aspirates and biopsies may be required at 2 to 3 month intervals to assess the response to treatment.

Excipient Information

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

4.5 Interaction with other medicinal products and other forms of interaction

Allopurinol

Allopurinol and pentostatin are both associated with skin rashes. Based on clinical studies in 25 refractory patients who received both pentostatin and allopurinol, the combined use of pentostatin and allopurinol did not appear to produce a higher incidence of skin rashes than observed with pentostatin alone. There has been a report of one patient who received both drugs and experienced a hypersensitivity vasculitis that resulted in death. It was unclear whether this adverse event and subsequent death resulted from the drug combination.

Vidarabine

Biochemical studies have demonstrated that pentostatin enhances the effects of vidarabine, a purine nucleoside with antiviral activity. The combined use of vidarabine and pentostatin may result in an increase in adverse reactions associated with each drug. The therapeutic benefit of the drug combination has not been established.

Fludarabine

The combined use of pentostatin and fludarabine phosphate is not recommended because it has been associated with an increased risk of fatal pulmonary toxicity. (See Section 4.4, Warnings).

Bone Marrow Transplant Regimen with high dose cyclophosphamide

Acute pulmonary oedema and hypotension leading to death, have been reported in the literature in patients treated with pentostatin in combination with carmustine, etoposide and high dose cyclophosphamide as part of an ablative regimen for bone marrow transplant. The combination of pentostatin and high dose cyclophosphamide is not recommended.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential receiving pentostatin should be advised not to become pregnant.

Due to the potential for genotoxicity and teratogenicity, female patients of reproductive potential are advised to use effective contraception during treatment and for at least 6 months following the last dose of pentostatin.

Due to the potential for genotoxicity, male patients with female partners of reproductive potential are advised to use effective contraception during treatment and for at least 3 months following the last dose of pentostatin.

Pregnancy

There are no data from the use of pentostatin in pregnant patients. Studies in animals have shown reproductive toxicity. Pentostatin has been shown to be teratogenic in rodent studies (See Section 5.3, Preclinical safety data). Pentostatin is not recommended in pregnancy and women of child bearing potential not using effective contraception. If the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazards to the foetus.

Breast-feeding

It is not known whether pentostatin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions due to pentostatin in nursing infants, the mother should be advised not to breast-feed while on pentostatin therapy and for 1 week following the last dose of treatment.

Fertility

No fertility studies have been conducted in animals. Incompletely reversible seminiferous tubular atrophy and degeneration in rats and in dogs may be indicative of potential effects on male fertility (See Section 5.3, Preclinical safety data). The possible adverse effects on human fertility have not been determined. It is recommended to discuss fertility preservation with men and women prior to treatment.

4.7 Effects on ability to drive and use machines

Pentostatin has a minor or moderate influence on the ability to drive and use machines. Patients should be advised to use caution in driving or using machinery following drug administration.

4.8 Undesirable effects

Pentostatin is lymphotoxic. Aside from myelosuppression, pentostatin is immunosuppressive in particular by suppression of the CD_4+ lymphocyte subset. CD_4+ counts smaller than 200 per µl are usually seen during treatment with pentostatin and CD_4+ count suppression can outlast the end of treatment by more than 6 months. With the exception of frequent herpes zoster infections the clinical consequences of the suppression of CD_4+ counts in hairy cell leukaemia are not well understood yet. Long term consequences are not predictable, but currently there is no evidence for higher frequency of secondary malignancies.

The following adverse events were reported during clinical studies in patients with hairy cell leukaemia who were refractory to alpha-interferon or were treated as front-line therapy. Most patients experienced an adverse event. The most commonly reported reactions were nausea and/or vomiting or leucopenia, each occurring in about 60% of patients. Fever, rash and fatigue were reported in about 40% of patients. Most adverse events were either mild or moderate diminished in frequency with continued therapy. Twelve percent of patients withdrew from treatment due to an adverse event. Many hairy cell leukaemia patients experience adverse events while under therapy with pentostatin. Given the natural history of the disease and the pharmacological properties of the drug it may be difficult in certain cases to discriminate between drug-related and disease-related adverse events. No extravasation injuries were reported in clinical studies.

The following adverse reactions have been reported during clinical studies in patients with HCL or during post-authorization use of pentostatin, either as single agent or in combinations with various agents for unapproved indications. They have been listed as Very common (> 10%), Common (1-10%), Uncommon (0.1-1%) or Rare (0.01-0.1%)

Body System	**Frequency**	**Adverse Reaction**
Infections and Infestations	Very common (> 10%)	Upper respiratory infection, Rhinitis, Pharyngitis, Viral infection
	Common[1] (1-10%)	Herpes Zoster, Infection (unspecified), Sinusitis, Cellulitis, Bacterial infection, Pneumonia, Conjunctivitis, Furunculosis, Herpes simplex, Bronchitis, Sepsis, Urinary tract infection, Abscess skin, Oral Candidiasis, Mycotic skin infection, Peri-anal abscess, E. Coli pneumonia, Fungal pneumonia, Septic shock, Staphylococcal infection, Urosepis, Osteomyelitis
	Uncommon[2] (0.1-1%)	Acute gastroenteritis, Pulmonary Aspergillosis, Clostridium Difficile colitis, Cystitis, Cytomegalovirus infection
	Rare[2] (0.01-0.1%)	Oesophageal candidiasis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Common[1] (1-10%)	Neoplasms, Skin carcinoma
	Uncommon[2] (0.1-1%)	Tumor lysis syndrome
Blood and Lymphatic System Disorders	Very common (> 10%)	Leucopenia, thrombocytopenia, Anaemia, Blood disorder, Eosinophilia, Hypochromic anaemia, Pancytopenia
	Common[1] (1-10%)	Agranulocytosis, Acute leukaemia, Febrile neutropenia, Ecchymosis, Lymphadenopathy, Splenomegaly
	Uncommon[2] (0.1-1%)	Pure red cell aplasia, Autoimmune haemolytic anaemia, Anaemia-Haemolytic, Aplastic anaemia haemolytic uremic syndrome, Idiopathic thrombocytopenia purpura, Thrombotic thrombocytopenia purpura.
	Rare[2] (0.01-0.1%)	Autoimmune thrombocytopenia
Immune System Disorders	Very common (> 10%)	Allergic reaction
	Common[1]	Graft versus Host Disease[3]

	(1-10%)	
	Uncommon[2] (0.1-1%)	Graft failure
	Rare[2] (0.01-0.1%)	Anaphylaxis
Metabolism and Nutrition Disorders	Common[1] (1-10%)	Dehydration, Gout, Electrolyte imbalance, Hypercalcaemia, Hyponatraemia, Hyperglycaemia, Weight increased, Weight decreased, LDH increased
	Uncommon[2] (0.1-1%)	Hyperkalaemia, Hypokalaemia, Oxygen saturation decreased
	Rare[2] (0.01-0.1%)	Fluid overload, Hypocalcaemia
Psychiatric disorders	Common[1] (1-10%)	Anxiety, Depression, Nervousness, Abnormal dreams, Decrease/loss libido, Emotional lability, Hallucination, Hostility, Neurosis, Thinking abnormal, Depersonalisation
Nervous System Disorders	Very common (> 10%)	Headache, Neurotoxicity
	Common[1] (1-10%)	Confusion, Dizziness, Insomnia, Paraesthesia, Somnolence, Amnesia, Ataxia, Convulsions, Dysarthria, Dysgeusia, Encephalitis, Hyperkinesia, Meningism, Neuralgia, Neuritis, Neuropathy, Paralysis, Syncope, Twitching, Tremor, Vertigo, Hypaesthesia
	Rare[2] (0.01-0.1%)	Dementia Alzheimer's (suspected), Grand mal convulsion, Migraine, Parkinson's disease (aggravated), Petit mal epilepsy
Eye Disorders	Common[1] (1-10%)	Dry eyes, Lacrimal disorder, Photophobia, Retinopathy, Vision abnormal, Fixed pupil, Lacrimation increased, Eye pain
	Rare[2] (0.01-0.1%)	Blepharitis
	Very rare	Unilateral uveitis with vision loss
Ear and Labyrinth Disorders:	Common[1] (1-10%)	Deafness, Ear pain, Labyrinthitis, Tinnitus
Cardiac Disorders	Common[1] (1-10%)	Angina pectoris, Arrhythmia, A-V block, Bradycardia, Extrasystoles ventricular, Heart arrest, Heart failure, Pericardial effusion, Sinus arrest, Tachycardia, Atrial fibrillation, Cardiac failure congestive, Flushing, Abnormal electrocardiogram.
	Uncommon[2] (0.1-1%)	Cardiomyopathy, Myocardial infarction
	Rare[2] (0.01-0.1%)	Pericarditis; Decreased ejection fraction
Vascular Disorders	Common[1] (1-10%)	Haemorrhage, Hypotension, Hypertension, Deep thrombophlebitis, Phlebitis, Vasculitis
	Uncommon[2] (0.1-1%)	Capillary leak syndrome
	Rare[2] (0.01-0.1%)	Shock
Respiratory, Thoracic and Mediastinal Disorders	Very common (> 10%)	Coughing, Lung disorder
	Common[1] (1-10%)	Asthma, Dyspnoea, Laryngeal oedema, Lung oedema, Pulmonary embolism, Epistaxis
	Uncommon[2] (0.1-1%)	Adult respiratory distress syndrome, Acute respiratory failure, Bronchospasm, Pleural effusion, Pneumothorax, Respiratory tract haemorrhage, Wheezing
	Rare[2] (0.01-0.1%)	Alveolitis, Alveolitis fibrosing, Cryptogenic organizing pneumonia, Diffuse alveolar damage, Obstructive airway disease, Pulmonary alveolar haemorrhage
Gastrointestinal Disorders	Very common (> 10%)	Nausea and/or vomiting; Diarrhoea, Abdominal pain, Anorexia, Rectal disorder, Rectal haemorrhage
	Common[1] (1-10%)	Dental Disorder, Dyspepsia, Gingivitis, Stomatitis, Constipation, Dysphagia, Flatulence, Glossitis, Ileus, Dry mouth
	Uncommon[2] (0.1-1%)	Acute enteritis

Hepato-biliary disorders	Very common (> 10%)	LFT increased, jaundice, hyperbilirubinaemia, ALT increased, AST increased
Skin and Subcutaneous Tissue Disorders	Very common (> 10%)	Rash, Pruritus, Sweating, Skin disorder, Maculopapular rash
	Common[1] (1-10%)	Dry skin, Urticaria, Acne, Alopecia, Eczema, Petechial Rash, Photosensitivity reaction, Exfoliative dermatitis, Skin discoloration, Dermatitis bullous, Seborrhoea
	Uncommon[2] (0.1-1%)	Angioneurotic oedema
	Rare	Pemphigus, Stevens-Johnsons's syndrome
Musculoskeletal and Connective Tissue Disorders	Very common (> 10%)	Myalgia, Bone disorder, Arthropathy
	Common[1] (1-10%)	Arthralgia, Arthritis
	Uncommon[2] (0.1-1%)	Pain in extremities
Renal and Urinary Disorders	Very common (> 10%)	Genito-urinary disorder, BUN increased
	Common[1] (1-10%)	Creatinine increased, Renal impairment, Nephropathy, Renal failure, Nephrolithiasis, Acute renal failure, Dysuria, Urinary retention
	Uncommon[2] (0.1-1%)	Cystitis haemorrhagic
Reproductive system and breast disorders:	Common[1] (1-10%)	Amenorrhoea, Breast mass, Erectile dysfunction
General Disorders and Administration Site Conditions	Very common (> 10%)	Fever, fatigue, chills, asthenia, pain
	Common[1] (1-10%)	Chest pain, Death, Face oedema, Peripheral oedema, Flu-like symptoms, Hangover, Back pain, Malaise
	Uncommon[2] (0.1-1%)	Mucositis, Multiorgan failure
	Rare[2] (0.01-0.1%)	Systemic inflammatory response syndrome, Lower extremity tenderness

[1]Includes all events which occurred in less than 3% of NIPENT-treated patients during the initial phase of the SWOG study:
[2]Based on 1549 patients included in post-marketing studies through Oct 10, 2005.
[3]Reported only in GVHD studies.

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 HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

No specific antidote for pentostatin overdose is known. Pentostatin administered at higher doses (20-50 mg/m2/course) than recommended was associated with deaths due to severe renal, hepatic, pulmonary, and CNS toxicity. In case of overdose, management would include general supportive measures through any period of toxicity that occurs.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Adenosine deaminase (ADA) inhibitor, ATC Code: LO1X X08

Mechanism of Action

Pentostatin is a potent transition state inhibitor of the enzyme adenosine deaminase. The greatest activity of ADA is found in cells of the lymphoid system with T-cells having higher activity than B- cells and T-cell malignancies higher ADA activity than B-cell malignancies. Pentostatin inhibition of ADA, as well as direct inhibition of RNA synthesis and increased DNA damage, may contribute to the overall cytotoxic effect of pentostatin. The precise mechanism of pentostatin's antitumour effect, however, in hairy cell leukaemia is not known.

Pentostatin has been shown to have activity against a variety of lymphoid malignancies, but is most active against indolent cancers with lower ADA concentration, such as hairy cell leukaemia.

5.2 Pharmacokinetic properties

In man, pentostatin pharmacokinetics are linear with plasma concentrations increasing proportionately with dose. Following a single dose of 4 mg/m^2 of pentostatin infused over 5 minutes, the distribution half-life was 11 minutes and the mean terminal half-life was 5.7 hours, with a range of 2.6 to 10 hours; the mean plasma clearance was 68 mL/min/m^2, and approximately 90% of the dose was excreted in the urine as unchanged pentostatin and/or metabolites as measured by adenosine deaminase inhibitory activity. The plasma protein binding of pentostatin is low, approximately 4%.

A positive correlation was observed between pentostatin clearance and creatinine clearance (CrCl) in patients with creatinine clearance values ranging from 60 mL/min to 130 mL/min. Pentostatin half-life in patients with renal impairment (CrCl < 50 mL/min, n = 2) was 18 hours, which was much longer than that observed in patients with normal renal function (CrCl > 60 mL/min, n = 14), about 6 hours.

Results from a published study in 13 patients with impaired renal function suggested dosage adjustment of NIPENT based on creatinine clearance (Clcr) values. Dosage was adjusted to 75% at a Clcr of 40-59 mL/min (3 mg/m^2) and to 50% at a Clcr of 35-39 mL/min (2 mg/m^2). There are insufficient data to recommend a starting or a subsequent dose for patients with creatinine clearance < 35 mL/min.

A tissue distribution and whole-body autoradiography study in the rat revealed that radioactivity concentrations were highest in the kidneys with very little central nervous system penetration.

Pentostatin penetrates the blood-brain barrier leading to measurable concentrations in the cerebrospinal fluid (CSF).

5.3 Preclinical safety data

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

Acute Toxicity

The combined-sex intravenous LD10, LD50 and LD90 values in mice given formulated pentostatin were 129, 300 and 697 mg/kg (387, 900, and 2091 mg/m^2), respectively.

Signs of acute toxicity in rodents and dogs were hypoactivity, dehydration, and emaciation. Lymphoid tissue was a principal target of pentostatin in rats and dogs; thymic atrophy and liver damage occurred in mice. There were no gonadal effects in rodents or dogs.

Multidose Toxicity

Five daily dose IV combined-sex LD10, LD50 and LD90 values in mice administered bulk pentostatin were 4.9, 6.4, and 8.3 mg/kg (14.8, 19.1, and 24.8 mg/m^2), respectively.

Regardless of route or duration of treatment, lymphoid tissue was the primary target of pentostatin in all species examined in toxicology studies. This is consistent with pentostatin's antineoplastic activity in hairy cell leukaemia. Effects of lymphoid tissue may be related to adenosine deaminase inhibition, the major pharmacologic action of pentostatin. Increased serum hepatic enzymes and liver changes in rodents and dogs indicate that the liver is also a target organ at high doses.

Incompletely reversible seminiferous tubular atrophy and degeneration in rats and in dogs may be indicative of potential effects on male fertility. Effects on lymphoid tissue, liver, and testes did not resolve completely during observation periods after drug withdrawal. Target organ effects occurring only in rats included alveolar duct metaplasia and/or goblet cell hyperplasia of the bronchioles, lymphoplasmacytic thyroiditis, and an increased incidence of spontaneous glomerulonephritis. Published studies, not conducted by the sponsor, indicate that pentostatin has immunosuppressive properties in mice and rats given multiple doses.

Mutagenesis

Pentostatin was not mutagenic in Salmonella typhimurium at concentrations up to 10000 µg/plate or in V79 Chinese hamster lung cells at concentrations up to 3000 µg/mL, in the presence or absence of metabolic activation. Pentostatin was not clastogenic in V79 Chinese hamster lung cells *in vitro* at concentrations up to 3000 µg/mL. However, pentostatin did increase the frequency of micronucleus formation in mice administered single intravenous injections of formulated pentostatin at 60, 360, and 720 mg/m^2. The relevance of the positive mouse micronucleus test for man is not known.

Carcinogenicity

The carcinogenic potential of pentostatin has not been evaluated. The possibility that Nipent causes tumours cannot be ruled out.

Pentostatin has been shown to be teratogenic from studies perfomed in rats and mice. Following systemic administration in rats, foetal abnormalities were observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Sodium hydroxide or Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

Acidic solutions should be avoided (the pH of the reconstituted powder is 7.0 to 8.2).

6.3 Shelf life

3 years

The reconstituted solution for injection or reconstituted and further diluted solution for infusion should be used within 8 hours and should not be stored above 25°C. Immediate administration after reconstitution is recommended.

6.4 Special precautions for storage

Store in a refrigerator (2 °C to 8 °C)

For storage conditions of the reconstituted medicinal product, see Section 6.3.

6.5 Nature and contents of container

NIPENT is supplied in single-dose, 10-mg vials packaged in individual cartons (packs of 1 vial).

Vials are made from Type I glass and siliconised stoppers.

6.6 Special precautions for disposal and other handling

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

Prescribers should refer to national or recognised guidelines on handling cytotoxic agents.

Procedures for proper handling and disposal of anticancer drugs should be followed.

1. Reconstitution of Nipent should only be carried out by trained personnel in a cytotoxic-designated area.
2. Adequate protective gloves should be worn.
3. The cytotoxic preparation should not be handled by pregnant staff.
4. Adequate care and precautions should be taken in the disposal of items syringes, needles etc. used to reconstitute cytotoxic drugs.
5. Contaminated surfaces should be washed with copious amounts of water.
6. Any remaining solution should be discarded.

Transfer 5 mL of Sterile Water for Injection to the vial containing NIPENT and mix thoroughly to obtain complete dissolution. The solution should be colourless to pale yellow and yield 2 mg/mL pentostatin. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

NIPENT may be given intravenously by bolus injection or diluted in a larger volume (25 to 50 mL) with 5% dextrose injection (5% glucose solution) or sodium chloride 9 mg/mL (0.9%) solution for injection (0.9% saline solution). Dilution of the entire contents of a reconstituted vial with 25 mL or 50 mL provides a pentostatin concentration of 0.33 mg/mL or 0.18 mg/mL, respectively, for the diluted solutions.

NIPENT solution when diluted for infusion with 5% dextrose injection (5% glucose solution) or sodium chloride 9 mg/mL (0.9%) solution for injection (0.9% saline solution) does not interact with PVC infusion containers or administration sets at concentrations of 0.18 mg/mL to 0.33 mg/mL.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0822/228/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

November 2025