Applicant/PHRC: ***Hetero Drugs South Africa (Pty). Ltd***

Product proprietary name: ***STINOHET 25 & 100***

Dosage form and strength: Powder for concentrate for solution for infusion

Each 10 mL vial contains 25 mg bendamustine hydrochloride

Each 20 mL vial contains100 mg bendamustine hydrochloride

PROPOSED PROFESSIONAL INFORMATION FOR STINOHET 25 & 100

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

STINOHET 25 (powder for concentrate for solution for infusion)

STINOHET 100 (powder for concentrate solution for infusion)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

STINOHET 25: Each 10 mL vial contains 25 mg bendamustine hydrochloride.

STINOHET 100: Each 20 mL vial contains 100 mg bendamustine hydrochloride.

1 mL of the concentrate contains 5 mg bendamustine hydrochloride of when reconstituted according to **Posology and method of administration** instructions.

STINOHET 25: Contains sugar – mannitol (42.50 mg)

STINOHET 100: Contains sugar – mannitol (170 mg)

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

STINOHET 25: White to off-white lyophilised powder.

STINOHET 100: White to off-white lyophilised powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

STINOHET is indicated for the following conditions:

- First-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.
- First-line treatment of indolent CD 20 positive non-Hodgkin's lymphoma in combination with rituximab
- Indolent non-Hodgkin's lymphomas as monotherapy in patients, who have progressed during or within 6 months following treatment with rituximab or a rituximab containing regimen.
- Front line treatment of multiple myeloma (Durie-Salmon stage II with progress or stage III) in combination with prednisone for patients older than 65 years who are not eligible for autologous stem cell transplantation and who have clinical neuropathy at time of diagnosis precluding the use of thalidomide or bortezomib containing treatment.

4.2 Posology and method of administration

Posology

Monotherapy for chronic lymphocytic leukaemia

100 mg/m^2 body surface area **STINOHET** on days 1 and 2; every 4 weeks.

Combination treatment for first-line indolent non-Hodgkin's lymphoma

90 mg/m^2 surface area **STINOHET** on days 1 and 2 in combination with 375 mg/m^2 body surface area rituximab as a slow i.v. infusion on day 1; every 4 weeks.

Monotherapy for indolent non-Hodgkin's lymphomas refractory to rituximab

120 mg/m^2 body surface area **STINOHET** on days 1 and 2; every 3 weeks.

Multiple Myeloma

120 – 150 mg/m^2 body surface area **STINOHET** on days 1 and 2, 60 mg/m^2 body surface area prednisone intravenous or orally on days 1 to 4; every 4 weeks.

Treatment should be terminated or delayed if leukocyte and/or platelet values dropped to ≤ 3 x 10^9/L or ≤ 75 x 10^9/L, respectively. Treatment can be continued after leukocyte values have increased to > 4 x 10^9/L and platelet values to > 100 x 10^9/L.

The leukocyte and platelet Nadir is reached, after 14 – 20 days with regeneration after 3 – 5 weeks. During therapy free intervals strict monitoring of the blood count is recommended (see section 4.4).

In case of non-haematological toxicity dose reductions have to be based on the worst CTC (common toxicity scale) grades in the preceding cycle. A 50 % dose reduction is recommended in case of CTC grade 3 toxicity. An interruption of treatment is recommended in case of CTC grade 4 toxicity.

If a patient requires a dose modification the individually calculated reduced dose must be given on day 1 and 2 of the respective treatment cycle.

Special populations

Elderly patients

There is no evidence that dose adjustments are necessary in elderly patients (see section 5.2).

Renal impairment

On the basis of pharmacokinetic data, no dose adjustment is necessary in patients with a creatinine clearance of > 10 mL/min. Experience in patients with severe renal impairment is limited.

Hepatic impairment

On the basis of pharmacokinetic data, no dose adjustment is necessary in patients with mild hepatic impairment [serum bilirubin < 2 mg/dL (34,2 µmol/L)].

A 30 % dose reduction is recommended in patients with moderate hepatic impairment (serum bilirubin [2 - 3,0 mg/dL (34,2 µmol/L - 51,3 µmol/L)].

No data is available in patients with severe hepatic impairment [serum bilirubin values of > 3,0 mg/dL (51,3 µmol/L)].

Paediatric population

There is no experience in children and adolescents with **STINOHET**

Method of administration

Precautions to be taken before manipulating or handing medicine

When handling **STINOHET**, inhalation, skin contact or contact with mucous membranes should be avoided (wear gloves and protective clothes). Contaminated body parts should be carefully rinsed with water and soap; the eye should be rinsed with physiological saline solution. If possible, it is recommended to work on special safety workbenches (laminar flow) with liquid impermeable, absorbing disposable foil. Pregnant personnel should be excluded from handling cytostatics.

For instructions on reconstitution of the medicine (see section 6.6).

STINOHET is administered by intravenous infusion over 30 – 60 min.

Infusion must be administered under the supervision of a physician qualified and experienced in the use of chemotherapeutic agents.

Poor bone marrow function is related to increased chemotherapy-induced haematological toxicity. Treatment should not be started if leukocyte and/or platelet values dropped to < 3 x 10^9/L or < 75 x 10^9/L, respectively (see section 4.3).

4.3 Contraindications

- Hypersensitivity to bendamustine or any of the excipients in **STINOHET.**
- Pregnancy and lactation.
- Severe hepatic impairment [serum bilirubin > 2,0 mg/dL (34,2 µmol/L)].
- Jaundice
- Severe bone marrow suppression and severe blood count alterations (leukocyte and/or platelet values dropped to < 3 x 10^9/L or < 75 x 10^9/L, respectively).
- Major surgery less than 30 days before the start of treatment.
- Infections, especially involving leukocytopenia.
- Yellow fever vaccination or any other live (attenuated) vaccination
- Congenital QT prolongation
- Concomitant medicines causing QT prolongation.

4.4 Special warnings and precautions for use

Myelosuppression

Patients treated with bendamustine hydrochloride experience myelosuppression. Treatment-related myelosuppression, leukocytes, platelets, haemoglobin, and neutrophils must be monitored at least weekly. Prior to the initiation of the next cycle of therapy, the following parameters are recommended:

Leukocyte and/or platelet values > 4 x 10^9/L or > 100 x 10^9/L, respectively.

Infections

Serious infection, including pneumonia and sepsis, has been reported with bendamustine hydrochloride. Infection has been associated with hospitalisation, septic shock and death. Patients with neutropenia and/or lymphopenia following treatment with bendamustine hydrochloride are more susceptible to opportunistic infections. Opportunistic infection such as Pneumocystis jirovecii pneumonia (PJP), varicella zoster virus (VZV) and cytomegalovirus (CMV) have been reported. Treatment with bendamustine hydrochloride may cause prolonged lymphocytopenia (< 600/µl) and low CD4-positive T-cell (T-helper cell) counts (< 200/µl) for at least 7–9 months after the completion of treatment. Lymphocytopenia and CD4-positive T-cell depletion is more pronounced when bendamustine is combined with rituximab. In case of low CD4-positive T-cell counts (< 200/µl) Pneumocystis jirovecii pneumonia (PJP) prophylaxis should be considered. Cases of tuberculosis have been less frequently reported compared to other infections. Latent or dormant tuberculosis may become active. (see section 4.8)

Patients with myelosuppression following **STINOHET** treatment should be advised to contact a medical practitioner if they have symptoms or signs of infection, including fever or respiratory symptoms. Discontinuation of bendamustine hydrochloride should be considered if there are signs of opportunistic infections. The presence of tuberculosis should be excluded before treatment with **STINOHET** is commenced.

Skin reactions

A number of skin reactions have been reported. These events have included rash, severe cutaneous reactions and bullous exanthema. Cases of Stevens – Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), some fatal, have been reported with the use of bendamustine hydrochloride. (see section 4.8).

Patients should be advised of the signs and symptoms of these reactions by their prescribers and should be told to seek medical attention immediately if they develop these symptoms. Some of these

events occurred when bendamustine hydrochloride was given in combination with other anticancer agents. Where skin reactions occur, they may be progressive and increase in severity with further treatment. If skin reactions are progressive, **STINOHET** should be withheld or discontinued. For severe skin reactions where a relationship to **STINOHET** is suspected, treatment should be discontinued.

Cardiac disorders

During treatment with **STINOHET** the concentration of potassium in the blood of cardiac patients must be closely monitored. When serum potassium levels are < 3,5 mEq/L, an ECG measurement must be performed, and potassium supplement must be given. Fatal cases of myocardial infarction and cardiac failure have been reported with bendamustine hydrochloride treatment. Patients with concurrent or history of cardiac disease should be observed closely.

Nausea, vomiting

An antiemetic should be given for the symptomatic treatment of nausea and vomiting.

Tumour lysis syndrome

Tumour lysis syndrome associated with bendamustine hydrochloride treatment has been reported in patients in clinical trials. The onset tends to be within 48 hours of the first dose of bendamustine hydrochloride and, without intervention, may lead to acute renal failure and death. Preventive measures include adequate volume status and close monitoring of blood chemistry, particularly potassium and uric acid levels. The use of allopurinol during the first one to two weeks of **STINOHET** therapy can be considered. However, there have been a few cases of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis reported when bendamustine hydrochloride and allopurinol are administered concomitantly.

Anaphylaxis

Infusion reactions to bendamustine hydrochloride have occurred commonly in clinical trials. Symptoms are generally mild and include fever, chills, pruritus and rash. Severe anaphylactic and anaphylactoid reactions have occurred. Patients must be asked about symptoms suggestive of infusion reactions after their first cycle of therapy.

Measures to prevent severe reactions, including antihistamines, antipyretics and corticosteroids must be considered in subsequent cycles in patients who have previously experienced infusion reactions. In patients who experienced Grade 3 or worse allergic-type reactions, **STINOHET** should be discontinued.

Contraception

Bendamustine hydrochloride is teratogenic and mutagenic. Women should not become pregnant during treatment. Male patients should not father a child during and up to 6 months after treatment. They should seek advice about sperm conservation prior to treatment with **STINOHET** because of possible irreversible infertility.

Extravasation

An extravasal injection should be stopped immediately. The needle should be removed after a short aspiration. Thereafter the affected area of tissue should be cooled. The arm should be elevated. Additional treatments like the use of corticosteroids are not of clear benefit. There have been reports of necrosis after accidental extra-vascular administration and toxic epidermal necrosis, tumour lysis syndrome, and anaphylaxis (see section 4.8).

Other malignancies

There have been reports of secondary tumours, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukaemia and bronchial carcinoma.

4.5 Interaction with other medicines and other forms of interaction

No *in vivo* interaction studies have been performed.

When **STINOHET** is combined with myelosuppressive agents, the effect of **STINOHET** and/or the co-administered medicinal products on the bone marrow may be potentiated. Any treatment reducing the patient's performance status or impairing bone marrow function can increase the toxicity of **STINOHET**.

Combination of **STINOHET** with ciclosporin or tacrolimus may result in excessive immunosuppression with risk of lymphoproliferation.

Cytostatics can reduce antibody formation following live-virus vaccination and increase the risk of infection which may lead to fatal outcome. This risk is increased in subjects who are already immunosuppressed by their underlying disease.

Bendamustine hydrochloride metabolism involves cytochrome P450 (CYP) 1A2 isoenzyme. Therefore, potential for interaction with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, acyclovir, and cimetidine exist.

CYP1A2 inducers, such as omeprazole, can reduce exposure to bendamustine.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

Women of childbearing potential must use effective methods of contraception both before and during **STINOHET** therapy.

Pregnancy

There is no adequate data from the use of **STINOHET** in pregnant women. In non-clinical studies bendamustine hydrochloride was embryo-/foetolethal, teratogenic and genotoxic. Therefore, **STINOHET** is contraindicated during pregnancy (see section 4.3).

Breastfeeding

It is not known whether bendamustine hydrochloride passes into the breast milk, therefore ǂ **STINOHET** is contraindicated during breastfeeding (see section 4.3). Breastfeeding must be discontinued during treatment with **STINOHET**.

Fertility

Men being treated with **STINOHET** are advised not to father a child during and for up to 6 months following cessation of treatment. Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with **STINOHET.**

4.7 Effects on ability to drive and use machines

Bendamustine hydrochloride may cause side effects such as ataxia, peripheral neuropathy and somnolence (see section 4.8). This may influence the ability to drive and use machines. Patients should be advised not to drive or operate machines if they experience these effects.

4.8 Undesirable effects

a. Summary of the safety profile

The most common adverse reactions with bendamustine hydrochloride are haematological adverse reactions (leukopenia, thrombopenia), dermatologic toxicities (allergic reactions), constitutional symptoms (fever), gastrointestinal symptoms (nausea, vomiting).

b. Tabulated list of adverse reactions

Infections and Infestations	
Frequent:	Infection (not otherwise specified), opportunistic infections (including Herpes zoster, cytomegalovirus, hepatitis B)
Less frequent:	Septicaemia, primary atypical pneumonia, Pneumocystis iiroveci pneumonia, tuberculosis (TB)
Neoplasm benign and malignant	
Frequent	Tumour lysis syndrome

Less frequent	Myelodysplastic syndrome, acute myeloid leukaemia
Blood and the lymphatic system disorders	
Frequent:	Leukopenia (not otherwise specified), thrombocytopenia, haemorrhage, anaemia, neutropenia, lymphopenia, myelosuppression
Less frequent:	Haemolysis, Pancytopenia, bone marrow failure.
Immune system disorders	
Frequent:	Hypersensitivity (not otherwise specified)
Less frequent:	Anaphylactic reaction, anaphylactoid reaction, anaphylactic shock
Nervous system disorders	
Frequent:	Insomnia, headache, dizziness
Less frequent:	Somnolence, aphonia, dysgeusia, paraesthesia, peripheral sensory neuropathy, anticholinergic syndrome, neurological disorders, ataxia, encephalitis
Cardiac disorders	
Frequent:	Cardiac dysfunction, such as palpitations, angina pectoris, dysrhythmia
Less frequent:	Pericardial effusion, tachycardia, myocardial infarction, cardiac failure

Frequency unknown	Atrial fibrillation
Vascular disorders	
Frequent:	Hypotension, hypertension
Less frequent:	Acute circulatory failure, phlebitis
Respiratory, thoracic and mediastinal disorders	
Frequent:	Pulmonary dysfunction
Less frequent:	Pulmonary fibrosis
Frequency unknown	Pneumonitis, pulmonary alveolar haemorrhage
Hepato-biliary disorders	
Frequency unknown	Hepatic failure
Gastrointestinal disorders	
Frequent:	Nausea, vomiting, diarrhoea, constipation, stomatitis, dry mouth
Less frequent:	Haemorrhagic oesophagitis, gastrointestinal haemorrhage
Skin and subcutaneous tissue disorders	
Frequent:	Alopecia, skin disorders (not otherwise specified)
Less frequent:	Erythema, dermatitis, pruritus, maculopapular rash, hyperhidrosis
Frequency unknown:	Bullous exanthema, Stevens – Johnson syndrome, Toxic Epidermal Necrolysis (TEN),

	drug reaction with eosinophilia and systemic symptoms (DRESS)*
Renal and urinary disorders	
Frequency unknown	Renal failure
Reproductive system and breast disorders	
Frequent:	Amenorrhoea
Less frequent:	Infertility
General disorders and administration site conditions	
Frequent:	Mucosal inflammation, fatigue, pyrexia, pain, chills, dehydration, anorexia
Less frequent:	Multiple organ failure
Investigations	
Frequent:	Decrease haemoglobin, increase creatinine, increase urea, Increase AST, increase ALT, increase alkaline phosphatase, increase bilirubin, hypokalaemia.

c. Description of selected adverse reactions

There have been isolated reports of necrosis after accidental extra-vascular administration and tumour lysis syndrome and anaphylaxis. The risk of myelodysplastic syndrome and acute myeloid leukemias is increased in patients treated with alkylating agents (including bendamustine). The secondary malignancy may develop several years after chemotherapy has been discontinued.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the risk/benefit ratio of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via '6.04 Adverse Drug Reactions Form' available online under SAHPRA's publications at https://www.sahpra.org.za/publications/Index/8/ or to the Holder of Certificate of Registration through the mail, pvg.cdma@heterodrugs.com. By reporting adverse reactions you can help provide more information on the safety of **STINOHET.**

4.9 Overdose

After application of a 30 min infusion of bendamustine hydrochloride once every 3 weeks the maximum tolerated dose (MTD) was 280 mg/m^2. Cardiac events of CTC (common toxicity scale) grade 2 which were compatible with ischaemic ECG changes occurred which were regarded as dose limiting.

In a subsequent study with a 30 min infusion of bendamustine hydrochloride at day 1 and 2 every 3 weeks the MTD was found to be 180 mg/m^2. The dose limiting toxicity was grade 4, thrombocytopenia. Cardiac toxicity was not dose limiting with this schedule.

Counter measures:

There is no specific antidote. Bone marrow transplantation and transfusions (platelets, concentrated erythrocytes) may be made, or haematological growth factors may be given as effective countermeasures to control haematological side effects. Bendamustine hydrochloride and its metabolites are dialysable to a small extent.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, alkylating agents, ATC code: L01AA09

Bendamustine hydrochloride is an alkylating antitumour agent. The antineoplastic and cytocidal effect of bendamustine hydrochloride is based essentially on a cross linking of DNA single and double strands by alkylation. As a result, DNA matrix functions and DNA synthesis and repair are impaired. The antitumour effect of bendamustine hydrochloride has been demonstrated by several *in vitro* studies in different human tumour cell lines (breast cancer, non-small cell and small cell lung cancer, ovarian carcinoma and various leukaemias) and *in-vivo* in different experimental tumour models with tumours of mouse, rat and human origin (melanoma, breast cancer, sarcoma, lymphoma, leukaemia and small cell lung cancer). Bendamustine hydrochloride showed an activity profile in human tumour cell lines different to that of other alkylating agents. The active substance revealed no or very low cross-resistance in human tumour cell lines with different resistance mechanisms at least in part due to a comparatively persistent DNA interaction. Additionally, it was shown in clinical studies that there is no complete cross-resistance of bendamustine with anthracyclines, alkylating agents or rituximab. However, the number of assessed patients is small.

5.2 Pharmacokinetic properties

Distribution

The elimination half-life $t_{1/2\beta}$ after 30 min intravenous infusion of 120 mg/m^2 area to 12 subjects was 28,2 minutes. Following 30 min intravenous infusion the central volume of distribution was 19,3 L. Under steady-state conditions following intravenous bolus injection the volume of distribution was 15,8 – 20,5 L.

More than 95 % of the substance is bound to plasma proteins (primarily albumin).

Biotransformation

A major route of clearance of bendamustine is the hydrolysis to monohydroxy- and dihydroxybendamustine. Formation of N-desmethyl-bendamustine and gamma-hydroxy-bendamustine by hepatic metabolism involves cytochrome P450 (CYP) 1A2 isoenzyme.

Another major route of bendamustine metabolism involves conjugation with glutathione.

In-vitro bendamustine does not inhibit CYP 1A4, CYP 2C9/10, CYP 2D6, CYP 2E1 and CYP 3A4.

Elimination

The mean total clearance after 30 min intravenous infusion of 120 mg/m^2 body surface area to 12 subjects was 639,4 mL/minute. About 20 % of the administered dose was recovered in urine within 24 hours. Amounts excreted in urine were in the order monohydroxy-bendamustine > bendamustine > dihydroxy-bendamustine > oxidised metabolite> N-desmethyl bendamustine. In the bile, primarily polar metabolites are eliminated.

Hepatic impairment

In patients with 30 to 70 % tumour infestation of the liver and mild or moderate hepatic impairment [serum bilirubin < 2,0 mg/dl (34,2 µmol/L)] the pharmacokinetic behaviour was not changed.

There was no significant difference to patients with normal liver and kidney function with respect to C_{max}, t_{max}, AUC, $t_{1/2\beta}$, volume of distribution and clearance. AUC and total body clearance of bendamustine correlate inversely with serum bilirubin.

Renal impairment

In patients with creatinine clearance > 10 mL/min including dialysis dependent patients, no significant difference to patients with normal liver and kidney function was observed with respect to C_{max}, t_{max}, AUC, $t_{1/2\beta}$, volume of distribution and clearance.

Elderly subjects

Subjects up to 84 years of age were included in pharmacokinetic studies. Higher age does not influence the pharmacokinetics of bendamustine.

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Mannitol

6.2 Incompatibilities

STINOHET must not be mixed with other medicinal products except those mentioned in section 4.2

6.3 Shelf life

36 months

Reconstituted concentrate:

The powder should be reconstituted immediately after opening of the vial.

The reconstituted concentrate should be diluted immediately with 0,9 % sodium chloride solution for injection.

Solution for infusion: {3 hours and 1 day indicated in dossier}

After reconstitution and dilution, chemical and physical stability has been demonstrated for 3,5 hours at 25 °C and 2 days at 2 °C to 8 °C in polyethylene bags.

From a microbiological point of view, the solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution or dilution see section 6.3

6.5 Nature and contents of container

STINOHET 25: 10 mL amber tubular Type 1 glass vial, with a grey rubber stopper and a blue flip off seal.

STINOHET 100: 20 mL amber tubular Type 1 glass vial, with a grey rubber stopper and a blue flip off seal.

6.6 Special precautions for disposal and other handling

The powder for concentrate for solution for infusion has to be reconstituted with water for injection, diluted with sodium chloride 9 mg/mL (0,9 %) solution for injection and then administered by intravenous infusion. Aseptic technique is to be used.

1. Reconstitution {Note: This reconstitution procedure is not possible with current vial sizes and quantity of water for injection indicated. This section is subject to P&A review and approval}

- Reconstitute each vial of **STINOHET** containing 25 mg bendamustine hydrochloride in 5 mL water for injection by shaking.
- Reconstitute each vial of **STINOHET** containing 100 mg bendamustine hydrochloride in 20 mL water for injection by shaking.

The reconstituted concentrate contains 5 mg bendamustine hydrochloride per mL and appears as a clear colourless solution.

2. Dilution

As soon as a clear solution is obtained (usually after 5 – 10 minutes) dilute the total recommended dose of **STINOHET** immediately with 0,9 % NaCl solution to produce a final volume of 500 mL.

STINOHET must be diluted with 0,9 % NaCl solution and not with any other injectable solution.

3. Administration

The solution is administered by intravenous infusion over 30 - 60 min.

The vials are for single use only.

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

Hetero Drugs South Africa (Pty). Ltd

Jean Park Chambers

252 Jean Avenue

Building 6, Unit 17 & 18

Centurion 0157

8 REGISTRATION NUMBER(S)

STINOHET 25: Will be allocated by the Authority upon registration.

STINOHET 100: Will be allocated by the Authority upon registration.

9 DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

To be advised.

10 DATE OF REVISION OF THE TEXT

To be advised.

DATE OF PUBLICATION OF PROFESSIONAL INFORMATION

To be allocated by the Authority upon registration.