1. **Proprietary name**
   NATULAN 50mg hard capsules

2. **Qualitative and quantitative composition**
   Each capsule contains:
   
   **Active ingredient**
   Procyclidine hydrochloride mg 58.3
   equal to procyclidine base mg 50

   Inactive ingredients, see section 6.1

3. **Pharmaceutical form**
   Hard capsules.

4. **Clinical information**
   4.1 **Therapeutic indications**
   Natulan is indicated in the treatment of: Hodgkin’s disease, lymphosarcoma, reticulosarcoma, Brill-Symmer’s disease.

   4.2 **Dosage and administration**
   NATULAN is administered orally, starting with low dose levels that are gradually increased up to the maximum dose of 250 or 300 mg daily.

   **Initial treatment schedule**
   
   1\textsuperscript{st} day 50 mg
   2\textsuperscript{nd} day 100 mg
   3\textsuperscript{rd} day 150 mg
   4\textsuperscript{th} day 200 mg
   5\textsuperscript{th} day 250 mg
   6\textsuperscript{th} day 250-300 mg
   following days 250-300 mg

   **Treatment continuation**
   Treatment with 250-300 mg daily should be continued until remission is as complete as possible; thereafter, the maintenance dose should be 50-150 mg daily. The treatment should not be discontinued before reaching a total dose of at least 6 grams, since results are difficult to assess below this threshold. If, during the initial phase of the treatment, leukocytes decrease to 3,000 units and thrombocytes to 80,000, the drug should be temporarily suspended. The administration of maintenance doses may be re-instated if leukocyte and thrombocyte values go up again. Therefore, it is particularly important to perform regular controls of the haematic status.

4.3 **Contraindications**
   Hypersensitivity to the drug or to any of its components.
   Pre-existing leukopenia and thrombocytopenia of a certain severity and of any etiopathogenesis, serious hepatic and renal lesions, pregnancy.
4.4 Special precautions
Permanent azoospermia and sterility have been reported. Procarbazine has been associated with secondary non-lymphoid neoplasias, including pulmonary cancer and acute leukemia, when used in combination therapy.
At the beginning of each cycle of procarbazine therapy blood test as well as a test of hepatic and renal function must be done.
The haematic status should be checked twice a week and hepatic and renal function at least once a week. Excessive toxicity has been found in patients with hepatic and/or renal disorders; these patients should start therapy in hospital.
Paediatric use: excessive toxicity including tremors, coma and convulsions has been reported. Dosage in children should be personalized. An attentive clinical monitoring is essential.

4.5 Interactions
Avoid alcohol (disulfiram- simil effect). Procarbazine is a mild monoamine oxidase inhibitor: possibility of interaction with food containing high levels of thyramine (such as cheese) and some drugs; sympathomimetics and decongestionants should be avoided.
Because of a possible potentiation of the effect the following drugs must be used with caution and at low dosages: central inhibitors (e.g. anaesthetics, barbiturates, narcotic analgesics), drugs with antocolinergic effect (including tricycle antidepressants), phenothiazine and antihypertensives.

4.6 Pregnancy and breast feeding
Procarbazine is contraindicated during pregnancy. Malformations have been reported in children borne to women exposed to procarbazine. Women of childbearing potential should avoid a pregnancy. It is not known whether procarbazine is excreted in human milk; however, due to the carcinogenic potential shown in animal studies with this molecule, breast feeding is not recommended for treated women.

4.7 Effects on driving and operating machinery
No such effects of the drug have been reported.

4.8 Adverse reactions
During the first days of treatment, lack of appetite and nausea are often observed, although these usually disappear after a short period.

With the administration of the drug the following adverse reactions have been reported:
Haematic and lymphatic disorders
Bone-marrow depression, leukopenia, thrombocytopenia, anemia, haemolitic anemia, pancytopenia, eosinophilia.

Gastrointestinal disorders
Nausea, vomiting, stomatitis, diarrhea, abdominal pain, constipation.

Nervous System disorders
Convulsions, neuropatia, paresthesia, cefalea.

Psychiatric disorders
hallucinations, depression, confusion, somnolence, psychosis.
Hepatobiliary disorders
hepatic dysfunction, hepatitis, jaundice

Respiratory disorders
Interstitial pneumonia.

Vascular disorders
Bleeding

Dermal and subcutaneous reactions
Urticaria, alopecia, rash, toxic epidermal necrolysis, Stevens-Johnson syndrome.

Immunitary disorders
Hypersensitivity reactions, including anaphylaxis and angioedema.

Metabolic disorders
Anorexia

Disorders of the reproductive system
Permanent azoospermia.

Neoplasias
Secondary non-lymphoid neoplasias, including pulmonary cancer and acute myelocytic leukemia, myelodysplasia.

Ocular disorders
Alterations of the vision.

Muskuloskeletal and tissutal disorders
Myalgia; necrosis of bones and ligaments.

Infections
Intercurrent infections, sepsis.

Systemic disorders
Pyrexia, asthenia.

4.9 Overdosage
After overdosage of procarbazine the following events have been reported: vertigo, nausea, vomiting, diarrhoea, hypotension, tachycardia, tremor, hallucinations, depression, convulsions. In this case an emetic must be given or, gastric lavage and intravenous rehydration therapy be started. Liver function and haematic status should be closely monitored for up to two weeks following the patient’s return to initial conditions. Anti-infective profylaxis should be considered.
Pharmacological characteristics

5.1 Pharmacodynamic characteristics
Pharmacotherapeutic category: Antineoplastics – Methylhydrazine
ATC code: L01XB01
Procarbazine is a yellowish crystalline powder that is soluble, though unstable, in water or aqueous solutions. The exact mechanism of action of procarbazine has not been identified, although this molecule seems to be able to inhibit the synthesis of proteins, RNA and DNA. Some studies suggest that procarbazine inhibits transmethylation of methionine methyl groups in t-RNA. The absence of active t-RNA may result in the inhibition of protein synthesis and thus RNA and DNA synthesis. Moreover, procarbazine can damage DNA directly. The hydrogen peroxide formed as a result of the drug self-oxidation can attack the sulfhydryl groups contained in the residual proteins closely bound to DNA.

5.2 Pharmacokinetic characteristics
Procarbazine is metabolized in the liver and kidneys, in a four-step sequence: oxidation, isomerization, hydrolysis and, again, oxidation, which leads to the formation of the inactive metabolite N-isopropyl-terephthalamic acid.
Procarbazine absorption is rapid and complete. After oral administration of 30 mg of 14C-labelled procarbazine, peak plasma concentration occurs within one hour. After intravenous administration, half life is approximately 10 minutes. Approximately 70% of the administered radioactivity is found in urine during the 24 hours that follow oral or intravenous administration of 14C-labelled procarbazine. After oral administration, procarbazine crosses the blood-brain barrier and rapidly reaches a steady-state level between plasma and liquor concentrations.

5.3 Pre-clinical safety data
The average lethal dose in laboratory animals ranges between 150 mg/kg in rabbits and 1300 mg/kg in mice.

Studies on mice, rats and monkeys show that procarbazine is carcinogenic, and has limited a mutagenic activity as shown in tests on bacteria and mammal cells.
Procarbazine is teratogenous as shown in studies on rats at doses 4-13 times the human recommended dosage.

6. Pharmaceutical information

6.1 List of inactive ingredients
Starch, talc, magnesium stearate, mannitol.

6.2 Incompatibility
See section 4.5.

6.3 Shelf-life
The shelf-life of the product is 3 years in the intact, correctly stored, packaging.

6.4 Special precautions for storage
None.
6.5 Packaging
Dark-glass bottle with screw-cap in thermoplastic material, contained in a carton box with
the patient information leaflet.
Bottle containing 50 capsules of 50 mg each

7 Marketing authorization holder
Sigma-Tau Industrie Farmaceutiche Riunite S.p.A.
Viale Shakespeare, 47 – 00144 Rome

8 Registration number
MA n. 020846010

9 Date of first authorization/Renewal
April 1967

10 Date of text revision
February 2006

11 Category according to law DPR 309/90
Not subject to the above law.

12 Distribution to the public
To be sold upon presentation of medical prescription.