

SUMMARY OF PRODUCT CHARACTERISTICS

1. Proprietary name

NATULAN 50mg hard capsules

2. Qualitative and quantitative composition

Each capsule contains:

Active ingredient

Procarbazine hydrochloride	mg	58.3
equal to procarbazine base	mg	50

Inactive ingredients, see section 6.1

3. Pharmaceutical form

Hard capsules.

4. Clinical information

4.1 Therapeutic indications

Natulán 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 st day	50	mg
2 nd day	100	mg
3 rd day	150	mg
4 th day	200	mg
5 th day	250	mg
6 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 tyramine (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 anticholinergic effect (including tricyclic 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, haemolytic 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, tachicardia, 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 prophylaxis should be considered.

5 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: oxydation, isomerization, hydrolysis and, again, oxydation, which leads to the formation of the inactive metabolite N-isopropyl-terephthamic 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.

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