# 1. NAME OF THE MEDICINAL PRODUCT

Natulan, capsules, hard 50 mg

# 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One Natulan capsule contains procarbazine hydrochloride, corresponding to 50 mg of procarbazine. For excipients, see section 6.1.

# 3. PHARMACEUTICAL FORM

Capsule, hard

# 4. CLINICAL PARTICULARS

## 4.1 Therapeutic indications

*Adults*
Natulan in combination chemotherapy is suitable for the treatment of Hodgkin's disease and non-Hodgkin's lymphoma. Natulan can also be used, as part of a combination therapy, for the treatment of brain tumours.

*Children*
Natulan is indicated in the treatment of Hodgkin's lymphoma in children aged 2-18, when associated with other antineoplastic drugs in an appropriate protocol.

## 4.2 Posology and method of administration

Treatment with Natulan must be administered under strict medical supervision.

Posology

*Adults*
Natulan is normally used in combination with two or more other cytostatics. Natulan forms part of many combination-chemotherapy programmes, such as MOPP (mechlorethamine, oncovin, procarbazine and prednisone). In this and in most other combination therapies, Natulan is administered in a daily oral dose of 100 mg/$m^2$ of body surface area.

*Paediatric population*
The pro m2 dose used in most published trials was analogous to the dose used in adults (100 mg/m2 for up to 14 days). The dose should be adjusted according to:

- The chemotherapy protocol used
- the functional state of the bone marrow
- previous chemo-and radiotherapy cycles
- the myelosuppressive effect of other cytostatics used.

The treatment and the maintenance doses of procarbazine should be determined only by a physician experienced in the use of potent antineoplastic drugs in children.

Method of administration
The capsules must be taken when standing or sitting. The capsules must not be chewed.

**Special populations**

*Patients with liver and renal impairment:*
Procarbazine should be used with caution in patients with hepatic or renal impairment, and is contra-indicated if impairment is severe. The haematological status of the patient should be determined at least every 3 or 4 days and hepatic and renal function determined weekly (see section 4.4).

*Elderly:*
Procarbazine should be used with caution in the elderly. Patients in this group should be observed very closely for signs of early failure or intolerance of treatment.

*Other special populations:*
Care is also advisable in patients with pheochromocytoma, epilepsy, or cardiovascular or cerebrovascular disease.

## 4.3 Contraindications

Natulan must not be given to patients:
- with severe leukocytopenia or thrombocytopenia. Patients who suffer from this condition as a result of chemotherapy or radiation therapy.
- with severe renal and hepatic failure
- who are breast-feeding (see section 4.6)
- with known hypersensitivity to procarbazine or one of the excipients.

## 4.4 Special warnings and precautions for use

It is recommended that procarbazine be given only under supervision of a physician experienced in the use of potent antineoplastic drugs.
Full blood count, and liver and renal function should be performed prior to each cycle of administration of procarbazine. The haematological status must be monitored twice a week and liver and renal function at least once a week. Increased toxicity has been reported in patients with decreased renal and/or hepatic function. Therapy initiation in hospital should be considered in these patients. Procarbazine is contraindicated if impairment is severe (see also section 4.3)

The immunosuppressant effect of procarbazine may increase the risk of infections caused by pathogenic or opportunistic micro-organism, may reduce the response to vaccines, and there is a possibility of generalized infection with live vaccines. Use of live vaccines should generally be avoided.

Secondary malignancies such as acute myeloid leukaemia and lung cancer have occurred in patients with Hodgkin's disease receiving procarbazine in combination with other chemotherapy and/or radiation therapy.
Discontinuation of treatment with procarbazine should be considered if the following situations occur:
- Leukopenia, Thrombocytopenia
- CNS symptoms such as paraesthesia, neuropathy or state of confusion
- Hypersensitivity reactions
- Severe diarrhoea
- Stomatitis
- Severe vomiting

Increased toxicity has been reported in children, including tremors, coma and convulsions. The dose should be individually determined and close clinical monitoring is essential.

The recommended daily dose of Natulan (100 mg/$m^2$) must be reduced by a third or a half, depending on the severity of the bone marrow depression with leukocytopenia and/or thrombocytopenia. Similar dose reductions must be applied in the event of nausea and vomiting.

If dose reductions in Natulan are needed, dose adjustments for the other combination therapy components must be considered as well since most of the cytostatics concerned cause similar undesirable effects on bone marrow and the gastrointestinal tract. Regular checks (every 2 to 3 days) of haematological values may be necessary in order to prevent severe leukocytopenia or thrombocytopenia and resultant infection and bleeding.

Permanent azoospermia has been reported. Male patients are therefore advised to have sperm frozen (cryopreservation) before the beginning of the treatment.

Warning: if the capsules are damaged, the unopened vial must be handed back to the treating physician or pharmacist. The appropriate guidelines on the handling and disposal of potent antineoplastic medicinal products should be followed.

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

Procarbazine may enhance the sedative effects of other CNS depressants.

Patients should be warned not to drink alcoholic beverages and to avoid food with high tyramine content.
Alcohol and alcoholic beverages combined with procarbazine can cause an antabuse syndrome (like disulfiram).
It may happen that patients who use Natulan develop alcohol intolerance. Abstinence from alcohol is necessary during the treatment.

As a weak monoamino-oxidase inhibitor, procarbazine potentiates the sedative effect of concomitantly administered sympathomimetics, decongestants, barbiturates, thymoleptics, neuroleptics, medicinal products with anticholinergic effects (including tricyclic antidepressants), anaesthetics, phenothiazines, narcotic analgesics and antihypertensive agents. If these drugs need to be used, they must be given with caution and in reduced dosage.

Eating cheese during treatment with monoamino-oxidase inhibitors may in rare cases cause an increase in blood pressure. Although this has never been reported during the use of Natulan, for safety considerations the patient should be advised not to eat food with high tyramine content such as cheese, yogurt or bananas during the treatment period.

Use of procarbazine with enzyme-inducing antiepileptics is associated with an increased risk of hypersensitivity reactions, possibly through a reactive intermediate generated by induction of the cytochrome P450 isoenzyme CYP3A subfamily. In patients with brain tumours who are treated with procarbazine, non-enzyme-inducing antiepileptics might be more appropriate.

## 4.6 Fertility, pregnancy and lactation

*Pregnancy*
There are very limited data on the use of procarbazine during pregnancy in humans. Following administration of procarbazine in pregnancy, usually in combination with other cytostatic agents, there have been reports both of children with abnormalities and of healthy children, even after administration in the first trimester
In animal studies (see section 5.3), procarbazine was shown to be teratogenic and fetotoxic. Use of procarbazine during pregnancy, especially in the first trimester, is advised against. In any individual case the expected benefits of treatment should be weighed against the possible risk for the fetus.

*Breast-feeding*
It is unknown whether procarbazine passes into breast milk in humans. Breast-feeding is contraindicated during the use of procarbazine.

*Fertility*
There is known to be a harmful effect on fertility.
Before starting treatment with procarbazine, both male and female patients have to be informed about the risk of sterility. Permanent azoospermia and sterility have been reported.

*Contraception*
During treatment both of men (see also section 4.4) and women, contraceptive measures should be taken for up to 3 months after the end of treatment.

## 4.7 Effects on ability to drive and use machines

There are no indications that Natulan reduces the ability to drive and use machines.

## 4.8 Undesirable effects

*Infections and infestations*
Intercurrent infections, sepsis

*Neoplasms, benign, malignant and non-specified (including cysts and polyps)*
Secondary non-lymphoid malignancies, including lung cancer and acute myelocytic leukaemia, myelodysplastic syndrome

*Blood and lymphatic system disorders*
Bone marrow depression, leukocytopenia, thrombocytopenia, anaemia, haemolytic anaemia, pancytopenia, eosinophilia

*Immune system disorders*
Hypersensitivity reactions, including anaphylaxis and angioedema

*Metabolism and nutrition disorders*
Anorexia

*Psychiatric disorders*
Hallucinations, depression, confusion, somnolence, psychosis

*Nervous system disorders*
Convulsions, neuropathy, paraesthesia, headache

*Eye disorders*
Vision disorders

*Vascular disorders*
Bleeding

*Respiratory, thoracic and mediastinal disorders*
Interstitial pneumonia

*Gastrointestinal disorders*
Nausea, vomiting, stomatitis, diarrhoea, abdominal pain, constipation

*Hepatobiliary disorders*
Impaired liver function, hepatitis, jaundice.

*Skin and subcutaneous tissue disorders*
Urticaria, alopecia, rash, toxic epidermal necrolysis, Stevens-Johnson syndrome,

*Musculoskeletal and connective tissue disorders*
Myalgia, necrosis of bone and joints

*Reproductive system and breast disorders*
Permanent azoospermia

*General disorders and administration site conditions*
Pyrexia, asthenia

## 4.9 Overdose

Symptoms
The following ADRs have been reported with overdose of procarbazine: nausea, vomiting, enteritis, seizures and coma, dizziness, hallucinations, bone marrow depression and convulsions. Hypotension, diarrhoea, tremors and tachycardia have also been observed in some cases.

Treatment
Absorption-reducing treatment (in the case of severe acute overdose: gastric lavage if given shortly after the overdose, administration of activated charcoal) and supportive symptomatic treatment. Following an overdose, a frequent check of the blood picture is advisable.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic category: antineoplastic drugs, methyl hydrazines
ATC-code: L01XB01
Procarbazine is an alkylating cytostatic agent that belongs to the class of methyl hydrazine compounds. Procarbazine intervenes in cell division (mitosis). This probably has an effect both on the already formed DNA and on DNA synthesis (methylation of purines, DNA-fragmentation). There is no cross-resistance with other cytostatics.

*Paediatric population*
Procarbazine in combination with other antitumour agents has been investigated in uncontrolled studies in children with brain tumours. Favourable partial responses, complete responses and survival rates have been documented. Paediatric data from randomized controlled clinical studies are limited.

### 5.2 Pharmacokinetic properties

*Absorption*
Procarbazine, the active substance of Natulan, is quickly and completely absorbed through the gastrointestinal tract. The peak plasma concentrations are reached 30-60 minutes after administration.

*Distribution*
Procarbazine diffuses into the cerebrospinal fluid. It is likely that procarbazine or its toxic metabolites pass through the placenta and into the breast milk.

*Biotransformation*
Procarbazine is quickly converted in both the liver and the kidneys, primarily into N-isopropyl terephthalic acid. Only about 5% of the administered dose appears in the urine in unchanged form. The efficacy of Natulan is partly attributed to the hydrogen peroxide and the hydroxyl radicals that are formed during the oxidative breakdown of procarbazine.

*Elimination*
Approximately 70% of the dose leaves the body via the urine within 24 hours, mainly as N-isopropyl terephthalic acid. The plasma elimination half-life is approximately 10 minutes.

*Pharmacokinetics in special situations*
Because of the limited renal excretion, an a priori dose reduction in patients with kidney disease is not necessary. In patients with anuria, the dose should be reduced.

### 5.3 Preclinical safety data

In toxicity studies in which repeated doses were given to rats and dogs, no other effects were found other than those that may be expected due to the pharmacological action mechanism, including atrophy of embryo testicular epithelium. Animal studies showed teratogenicity and reproduction toxicity. Furthermore, mutagenicity and carcinogenicity were shown.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Capsule content: mannitol (E421), maize starch, talc (E553b), magnesium stearate (E572)
Capsule wall: yellow iron oxide (E172), titanium dioxide (E171), gelatin.

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

Store below 25°C.

### 6.5 Nature and contents of container

Brown glass bottle containing 50 capsules, fitted with an HDPE stopper with a desiccant capsule.

Alu/alu blister pack of 50 capsules (5 blisters with 10 capsules each) in a carton box.

### 6.6 Special precautions for disposal

No special requirements.

## 7 MARKETING AUTHORISATION HOLDER

Leadiant GmbH
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## 8. MARKETING AUTHORISATION NUMBER(S)

RVG 05077

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07 October 1966
Date of latest renewal: 07 October 2016

## 10. DATE OF REVISION OF THE TEXT

Latest partial revision section 7: