1 NAME OF THE MEDICINAL PRODUCT
Procarbazine 50mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 58.3mg Procarbazine hydrochloride (equivalent to 50mg of Procarbazine).
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Capsules with white opaque cap and body. Marked ‘CL50’ on one half.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The main indication is Hodgkin's disease (lymphadenoma).

Procarbazine may also be useful in other advanced lymphomata and a variety of solid tumours which have proved resistant to other forms of therapy.

Children

Procarbazine 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

In combination chemotherapeutic regimens:

Procarbazine is usually administered concomitantly with other appropriate cytostatic drugs in repeated four- to six-weekly cycles. In most such combination chemotherapy regimens currently in use (eg. the so-called MOPP schedule with mustine, Vincristine and Prednisone) Procarbazine is given daily on the first 10 - 14 days of each cycle in a dosage of 100mg per sq. metre of body surface (to nearest 50mg).

As sole therapeutic agent: Adults:
Treatment should begin with small doses which are increased gradually up to a maximum daily dose of 250 or 300mg divided as evenly as possible throughout the day.

Initial dosage scheme

<table>
<thead>
<tr>
<th>Day</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>50mg</td>
</tr>
<tr>
<td>2nd</td>
<td>100mg</td>
</tr>
<tr>
<td>3rd</td>
<td>150mg</td>
</tr>
<tr>
<td>4th</td>
<td>200mg</td>
</tr>
<tr>
<td>5th</td>
<td>250mg</td>
</tr>
</tbody>
</table>

Further procedure:

Treatment should be continued with 250 or 300mg daily until the greatest possible remission has been obtained, after which a maintenance dose is given.

Maintenance dose:

50 -150mg daily. Treatment should be continued until a total dose of at least 6g has been given. Otherwise, a negative result is not significant.

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.

Children:

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.

Procarbazine capsules are for oral administration.

### 4.3 Contraindications

Pre-existing severe leucopenia or thrombocytopenia from any cause; severe hepatic or renal damage.

Procarbazine should not be used in the management of non-malignant disease.

Procarbazine is contraindicated during the first trimester of pregnancy and during breast-feeding (see section 4.6).
Hypersensitivity to the active substance (Procarbazine) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Procarbazine should be given only under the supervision of a physician who is experienced in cancer chemotherapy and having facilities for regular monitoring of clinical and haematological effects during and after administration.

Introduction of therapy should only be effected under hospital conditions.

Caution is advisable in patients with hepatic or renal dysfunction and Procarbazine should be avoided in patients with severe hepatic or renal disease. Its use should be avoided if creatinine clearance is less than 10mL/min. Caution is also advised in cardiovascular or cerebrovascular disease, phaeochromocytoma, or epilepsy.

Regular blood counts are of great importance due to the possibility of bone-marrow suppression. If during the initial treatment the total white cell count falls to 3,000 per mm$^3$ or the platelet count to 80,000 per mm$^3$, treatment should be suspended temporarily until the leucocyte and/or platelet levels recover, when therapy with the maintenance dose may be resumed.

Treatment should be interrupted on the appearance of allergic skin reactions.

Live vaccines should not be given during or within at least 6 months of treatment with immunosuppressive chemotherapy or radiotherapy for malignant disease.

4.5 Interaction with other medicinal products and other forms of interaction

Procarbazine is a weak MAO inhibitor and therefore interactions with certain foodstuffs and drugs, although very rare, must be borne in mind. Thus, owing to possible potentiation of the effect of barbiturates, narcotic analgesics (especially Pethidine), drugs with anticholinergic effects (including phenothiazine derivatives and tricyclic antidepressants), other central nervous system depressants (including anaesthetic agents) and anti-hypertensive agents, these drugs should be given concurrently with caution and in low doses.

Cytotoxics may reduce the absorption of phenytoin and cardiac glycosides.

Concomitant use of clozapine may increase the risk of agranulocytosis. Use with enzyme-inducing antiepileptics is associated with an increased risk of hypersensitivity reactions to procarbazine.

Intolerance to alcohol (Disulfiram-like reaction) may occur.
4.6 Fertility, pregnancy and lactation

Pregnancy
Use of Procarbazine is contraindicated during the first trimester of pregnancy, and should be avoided throughout the remainder of the gestational period.

Studies in animals have shown reproductive toxicity (see 5.3). The potential risk for humans is unknown. There are no adequate data from the use of Procarbazine in pregnant women, however isolated human foetal malformations have been reported following MOPP combination therapy.

Breast-feeding
Procarbazine is contraindicated during breast-feeding.

Fertility
Procarbazine has been reported to cause azoospermia and ovarian failure, which may be irreversible. It is extremely important that the patient is provided with appropriate information and advice, particularly as men may wish to have semen saved for use after Procarbazine treatment (see section 4.8).

4.7 Effects on ability to drive and use machines

Patients should be warned of the possibility of lethargy (see section 4.8 Undesirable effects).

4.8 Undesirable effects

Tabulated list of adverse reactions

Undesirable effects are listed by MedDRA System Organ Classes.

Assessment of undesirable effects is based on the following frequency groupings:

Very common: $\geq 1/10$
Common: $\geq 1/100$ to $<1/10$
Uncommon: $\geq 1/1,000$ to $<1/100$
Rare: $\geq 1/10,000$ to $<1/1,000$
Very rare: $<1/10,000$
Not known: cannot be estimated from the available data

<p>| Infections and infestations | Not known: Infections (see section 4.4) |</p>
<table>
<thead>
<tr>
<th>Blood and lymphatic systems disorders</th>
<th>Not known: Leucopenia, Thrombocytopenia, Neutropenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Not known: Severe hypersensitivity reactions with angioedema, urticaria and a precipitous drop in serum complement</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Not known: Lethargy</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Not known: Pneumonitis</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Very common: Loss of appetite, Nausea, Vomiting</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Not known: Hepatic complications including jaundice and abnormal liver function tests</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Not known: Allergic skin reactions</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Not known: Azoospermia, Ovarian failure</td>
</tr>
</tbody>
</table>

Description of selected adverse reactions

Leucopenia and thrombocytopenia are almost always reversible and seldom require complete cessation of therapy.

Loss of appetite, nausea and vomiting are usually confined to the first few days of treatment and then tend to disappear.

Azoospermia and ovarian failure may be irreversible. It is extremely important that the patient is provided with appropriate information and advice, particularly as men may wish to have semen saved for use after Procarbazine treatment.

Procarbazine is carcinogenic and an increased incidence of acute myelogenous leukaemia has been reported in patients receiving MOPP chemotherapy for Hodgkins disease.

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 Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Signs of overdosage include severe nausea and vomiting, dizziness, hallucinations, depression and convulsions; hypotension or tachycardia may occur.

The benefit of gastric decontamination is uncertain. Consider activated charcoal if the patient presents within 1 hour of ingestion of any amount (because of risk of myelosuppression at all doses).

General supportive treatment should be performed, with prophylactic treatment against possible infection, and frequent blood counts weekly for at least 3 weeks, or more frequently if unwell or clinically symptomatic from myelosuppression (evidence of bleeding or infection).

Consider further haematological monitoring after 3 weeks only if white cells and platelets not recovering (discuss with haematologist/oncologist).

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Methylhydrazines, ATC Code: L01XB01

Procarbazine, a methylhydrazine derivative, is a cytostatic agent with weak MAO inhibitor properties. Its exact mode of action on tumour cells is unknown. It may be effective in patients who have become resistant to radiation therapy and other cytostatic agents.

Children:

Procarbazine in combination with other anti-tumour 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 randomised controlled clinical studies are limited.

5.2 Pharmacokinetic properties

Absorption
Procarbazine is readily absorbed from the gastrointestinal tract.

Distribution
Peak plasma levels are reached at 0.5-1 hour after oral administration. Procarbazine quickly equilibrates between the blood and cerebrospinal fluid (CSF). Peak CSF levels are achieved 30-90 minutes after oral administration.

Biotransformation
Procarbazine is rapidly metabolised, the primary circulating metabolite is the azo derivative while the major urinary metabolite has been shown to be N-isopropyl-terephthalamic acid.

Elimination
A plasma half-life of about 10 minutes has been reported.

Approximately 5% of procarbazine is excreted unchanged in the urine. The remainder is oxidised to N-isopropylterephthalamic acid and excreted in the urine, up to about 70% of a dose being excreted in 24 hours. Some of the drug is excreted as carbon dioxide and methane via the lungs.

5.3 Preclinical safety data
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction, other than already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Mannitol
Maize starch
Talc
Magnesium stearate

Capsule shell components:
Gelatin
Titanium dioxide E171

Ink components:
Shellac
Propylene glycol
Ammonium hydroxide
Black iron oxide E172

6.2 Incompatibilities
Not applicable.
6.3 Shelf life
Three years.

6.4 Special precautions for storage
Store in a dry place. Do not store above 25°C.

6.5 Nature and contents of container
Blister packs of 50 capsules.

6.6 Special precautions for disposal and other handling
Handling guidelines:

Undamaged capsules present minimal risk of contamination, but in accordance with good hygiene requirements, direct handling should be avoided. As with all cytotoxics, precautions should be taken to avoid exposing staff during pregnancy.

Urine produced for up to 48 hours after a dose of procarbazine should be handled wearing protective clothing.

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

7 MARKETING AUTHORISATION HOLDER
Alliance Pharmaceuticals Limited
Avonbridge House
Bath Road
Chippenham
Wiltshire,
SN15 2BB
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 16853/0114
9  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   30/08/2006

10  DATE OF REVISION OF THE TEXT
    05/01/2015