MAVENCLAD®

10 mg Tablets (cladribine)

Prescriber's Guide

IMPORTANT INFORMATION ON MINIMISING THE RISK OF ADVERSE EVENTS

Reporting Adverse Events

Adverse events should be reported. In the Republic of Ireland, suspected adverse reactions should be reported via HPRA Pharmacovigilance: **www.hpra.ie**.

Adverse events should also be reported to Merck Serono Limited – Tel: 1 800 719 881 or email: **medinfo.uk@merckgroup.com**.

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Please note that this material does not contain all the information related to the adverse event profile of MAVENCLAD®, or the relevant prescribing information. Please refer to the Summary of Product Characteristics for more detailed guidance.

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Introduction to MAVENCLAD®

This guide provides information on the most important risks associated with MAVENCLAD® and the activities required to minimise these risks.

The patient guide is part of the risk minimisation measures, and use of the material in your discussion with the patient, may support the early identification of signs and symptoms of potential adverse reactions and their timely treatment.

This guide should be read in conjunction with the information provided in the approved summary of product characteristics (SmPC) of MAVENCLAD®. Careful consideration should be given to the information in the SmPC regarding blood tests and screening for latent infections before initiating treatment.

Treatment regimens

MAVENCLAD® therapy consists of two treatment courses administered at the beginning of two consecutive treatment years. Each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective year. The dose administered is dependent on the individual patient's body weight (see Table 1).

	MONTH 1	MONTH 2	MONTHS 3-12
YEAR 1	4-5 DAYS TREATMENT	4-5 DAYS TREATMENT	NO FURTHER TREATMENT WITH MAVENCLAD® IS REQUIRED IN YEAR 1
YEAR 2	4-5 DAYS TREATMENT	4-5 DAYS TREATMENT	NO FURTHER TREATMENT WITH MAVENCLAD® IS REQUIRED IN YEAR 2
YEAR 3	NO FURTHER TREATMENT WITH MAVENCLAD® IS REQUIRED IN YEAR 3		
YEAR 4	NO FURTHER TREATMENT WITH MAVENCLAD® IS REQUIRED IN YEAR 4		

Following completion of the 2 treatment courses in two consecutive years, no further cladribine treatment is required in years 3 and 4.

MAVENCLAD® tablets are packed in a reclosable, child resistant carton. The package leaflet will include a step-by-step guide on how to handle the package and take MAVENCLAD® tablets.

The number of MAVENCLAD® tablets is calculated according to the body weight of the patient. Table 1 provides the number of MAVENCLAD® tablets to be taken each week over the two weekly treatment periods in each of the two years.

In order to prevent medication errors, it is recommended that you prescribe your patient the exact number of tablets he/she will need for one week of treatment only. Please note that this may require prescription of more than one pack size based on the patient's body weight, as not all pack sizes may be marketed in all countries. Pack sizes of 1, 4, and 6 will be marketed in UK and Ireland. Please also note that the number of tablets needed differs from one treatment week to the next for patients with a body weight of 80 kg up to < 110 kg.

The 1-tablet pack size can be used to complement the required number of tablets, but also as a replacement e.g. in case the patient loses a tablet.

Table 1: Dose of MAVENCLAD® per year and week by patient body weight

	DOSE IN MG (NUMBER OF 10 MG TABLETS) PER WEEK	
RANGE OF BODY WEIGHT	TREATMENT WEEK 1 (FIRST MONTH)	TREATMENT WEEK 2 (SECOND MONTH)
40 to < 50 kg	40 mg (4 tablets)	40 mg (4 tablets)
50 to < 60 kg	50 mg (5 tablets)	50 mg (5 tablets)
60 to < 70 kg	60 mg (6 tablets)	60 mg (6 tablets)
70 to < 80 kg	70 mg (7 tablets)	70 mg (7 tablets)
80 to < 90 kg	80 mg (8 tablets)	70 mg (7 tablets)
90 to < 100 kg	90 mg (9 tablets)	80 mg (8 tablets)
100 to < 110 kg	100 mg (10 tablets)	90 mg (9 tablets)
110 kg and above	100 mg (10 tablets)	100 mg (10 tablets)

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The numbers of tablets to be taken each day to achieve the total weight dependent dose are shown in the following table.

Table 2: MAVENCLAD® 10 mg tablets per week day

Total tablets per week	Day 1	Day 2	Day 3	Day 4	Day 5
4	1	1	1	1	0
5	1	1	1	1	1
6	2	1	1	1	1
7	2	2	1	1	1
8	2	2	2	1	1
9	2	2	2	2	1
10	2	2	2	2	2

If a daily dose consists of two tablets, both tablets are taken together as a single dose. The daily dose should be taken at intervals of 24 hours at approximately the same time each day.

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Monitoring during treatment

Lymphocyte counts

MAVENCLAD®'s mode of action is closely linked to a reduction in lymphocyte count. In clinical studies when MAVENCLAD® was used as a monotherapy at a cumulative dose of 3.5 mg/kg the incidence of lymphopenia was very common (≥1/10). In these clinical studies, 20% to 25% of the patients developed transient grade 3 or 4 lymphopenia (<500 to 200 cells/mm^3 or <200 cells/mm^3). Grade 4 lymphopenia was seen in less than 1% of the patients. It is expected that most patients recover to either normal lymphocyte counts or grade 1 lymphopenia within 9 months. To decrease the risk for severe lymphopenia, lymphocyte counts must be determined before, during and after cladribine treatment.

A lymphocyte count test must be performed

- before initiating MAVENCLAD® in year 1,
- before initiating MAVENCLAD® in year 2,
- 2 and 6 months after start of treatment in each treatment year. If the lymphocyte count is below 500 cells/mm^3 it should be actively monitored until values increase again.

Before start of initial treatment, the patient's lymphocyte count must be within the normal range. Before the start of the treatment course in year 2, it must be at least 800 cells/mm^3. If necessary, administration of MAVENCLAD® in year 2 can be postponed for up to 6 months to allow for a recovery of lymphocyte count. No treatment should be given in year 2 and MAVENCLAD® should be withdrawn if recovery does not occur within these 6 months.

If lymphocyte counts drop below 200 cells/mm^3, consider anti-herpes prophylaxis of your patient until the value returns to more than 200 cells/mm^3.

Liver values

Liver injury, including serious cases, has been reported in patients treated with MAVENCLAD®. Before initiating MAVENCLAD® a comprehensive patient history regarding previous episodes of liver injury with other drugs or underlying liver disorders should be taken.

The following tests should be performed before start of treatment in year 1 and year 2:

- Serum aminotransferases
- Total bilirubin
- Alkaline phosphatase

If a patient develops clinical signs, including unexplained liver enzyme elevations, or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, jaundice and/or dark urine), promptly measure serum transaminases and total bilirubin. Interrupt or discontinue treatment with MAVENCLAD®, as appropriate.

Severe infections

Like other agents that affect the immune system, cladribine can reduce the body's immune defence and may increase the likelihood of infections. The risk of infections should be discussed with the patient. Human immunodeficiency virus (HIV) infection must be excluded before initiation of treatment with MAVENCLAD®. Patients with active chronic infections such as tuberculosis and hepatitis must not be treated with MAVENCLAD®. Screening for latent infections, in particular hepatitis B and C and tuberculosis must be performed prior to starting MAVENCLAD® treatment in year 1 and year 2. Initiation of MAVENCLAD® should be delayed until the infection has been adequately treated and is fully controlled.

Patients with a lymphocyte count below 500 cells/mm^3 should be actively monitored for infections. Patients on MAVENCLAD® treatment must be carefully monitored for signs and symptoms suggestive of any infection, in particular herpes zoster (common adverse reaction [≥1/100 to <1/10]) and opportunistic infections including reactivation of tuberculosis (very rare [<1/10,000]). If signs and symptoms suggestive of an infection occur, anti-infective treatment, including appropriate antiviral therapies, should be initiated as clinically indicated. Interruption or delay of MAVENCLAD® therapy may be considered until proper resolution of the infection.

Progressive multifocal leukoencephalopathy (PML)

In clinical trials with multiple sclerosis patients treated with MAVENCLAD® (1,976 patients, 8,650 patient years), no case of PML has been reported. PML cases have been reported for parenteral cladribine in patients treated for hairy cell leukaemia with a different treatment regimen.

Patients should be informed about the potential risk of PML with MAVENCLAD® and should be informed of early signs and symptoms suggestive of PML.

A baseline magnetic resonance imaging (MRI) scan should be performed before initiating MAVENCLAD®, usually within 3 months. During subsequent routine MRI scans, physicians should pay attention to lesions suggestive of PML.

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PML can only occur in the presence of JC virus infection. If an anti-JC virus antibody test is done, it should be borne in mind that the influence of lymphopenia on the accuracy of such tests has not been studied in patients treated with MAVENCLAD®. Physicians should note that a negative antibody test in the presence of normal lymphocyte count does not preclude the possibility of current or subsequent JC virus infection.

Malignancies

MS patients with current malignancies must not be treated with MAVENCLAD®. Single instances of malignancy have been observed in patients who had received cladribine in clinical studies. Patients should be advised to follow standard cancer screening guidelines after treatment.

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Prevention of pregnancy

Since MAVENCLAD® is known to inhibit DNA synthesis and is embryolethal in pregnant mice and teratogenic in mice and rabbits, female patients and female partners of male patients being treated with MAVENCLAD® need to be counselled before initiation of treatment both in year 1 and year 2 regarding the potential for serious risk to the foetus and the need for effective contraception to avoid becoming pregnant.

If a pregnancy nevertheless occurs in association to MAVENCLAD® treatment, please report it to **GDS@merckgroup.com**. You may be contacted by Merck Drug Safety staff to ensure that any relevant follow-up information is captured.

Information for Female Patients

Inform female patients that use of MAVENCLAD® is prohibited in pregnant women because of the risk of serious harm to the unborn foetus. Pregnancy must be excluded before start of therapy with MAVENCLAD® in year 1 and year 2. Inform female patients of childbearing potential that they must prevent pregnancy by use of an effective contraceptive method (i.e. a method with a failure rate of less than 1% per year when used consistently and correctly) during MAVENCLAD® treatment and for at least 6 months after the last dose of MAVENCLAD® in each treatment year.

Female patients who become pregnant during these periods should be told to inform their prescribing physician as soon as possible in order that appropriate counselling can be undertaken. Provide guidance to patients about effective contraceptive methods. Awareness should be exercised when starting hormonal contraception that full effectiveness is not given from the very beginning (please refer to respective product information).

MAVENCLAD® does not reduce the effectiveness of systemically acting hormonal contraceptives.

Information for Male Patients

Inform male patients that MAVENCLAD® can be transferred to their female partner via their semen and could cause harm to the unborn foetus. Therefore, pregnancy of their partner must be prevented during MAVENCLAD® treatment and for at least 6 months after the last dose of MAVENCLAD®, by using an effective method of contraception (i.e. a method with a failure rate of less than 1% per year when used consistently and correctly). If female partners do become pregnant during these periods, they should be told to inform their physician as soon as possible in order that appropriate counselling can be undertaken.

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