PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

# PrMAVENCLAD™

Cladribine

10 mg Tablet

Selective Immunosuppressant

**Treatment with MAVENCLAD should be initiated and supervised by neurologists experienced in the treatment of patients with MS and who have fully familiarised themselves with the efficacy and safety profile of MAVENCLAD.**

EMD Serono, a Division of EMD Inc., Canada
2695 North Sheridan Way, Suite 200
Mississauga, Ontario L5K 2N6
www.emdserono.ca
EMD Serono is a business of Merck KGaA, Darmstadt, Germany

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## Table of Contents

# [Pr]MAVENCLAD™

Cladribine

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Nonmedicinal Ingredients |
|---|---|---|
| Oral | Tablet / 10 mg | Hydroxypropyl betadex, sorbitol, magnesium stearate |

### INDICATIONS AND CLINICAL USE

**Adults:**
MAVENCLAD (cladribine) is indicated as monotherapy for the treatment of adult patients with relapsing-remitting multiple sclerosis (RRMS) to reduce the frequency of clinical exacerbations and delay the progression of disability. MAVENCLAD is generally recommended in MS patients who have had an inadequate response to, or are unable to tolerate, one or more therapies for multiple sclerosis.

MAVENCLAD treatment should be initiated and supervised by neurologists experienced in the treatment of MS and who have fully familiarized themselves with the efficacy and safety profile of MAVENCLAD and are able to discuss benefits/risks with patients.

The efficacy of taking MAVENCLAD for treatment duration beyond 2 years has not been established.

**Geriatrics (> 65 years of age):**
Clinical studies of MAVENCLAD in MS did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).

**Pediatrics (< 18 years of age):**
The safety and efficacy of MAVENCLAD in patients below the age of 18 years have not been studied. MAVENCLAD is not indicated in patients below 18 years of age.

## CONTRAINDICATIONS

MAVENCLAD is contraindicated in:

- Patients who are hypersensitive to cladribine or to any ingredient in the formulation or component of the container. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.
- Patients with increased risk for opportunistic infections, including those who are immunocompromised due to treatment (e.g. immunosuppressive or immunomodulating therapies, antineoplastic, myelosuppressive therapies, total lymphoid irradiation or bone marrow transplantation) (see DRUG INTERACTIONS) or disease (e.g. immunodeficiency syndrome).
- Patients with latent or active infections including active chronic bacterial, fungal or viral infections (e.g. hepatitis, tuberculosis).
- Patients with a history of progressive multifocal leukoencephalopathy (PML).
- Patients with active malignancy.
- Patients with moderate or severe renal impairment (creatinine clearance < 60 mL/min) (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Excretion).
- Patients who are pregnant or breast-feeding (see WARNINGS AND PRECAUTIONS, Special Populations).

## WARNINGS AND PRECAUTIONS

### General

Before initiating treatment with MAVENCLAD:

- Check complete blood count (CBC), including lymphocyte count, before starting therapy if no recent (i.e. within 6 months or after discontinuation of prior therapy) result is available (see WARNINGS AND PRECAUTIONS, Hematologic; DOSAGE AND ADMINISTRATION).
- MAVENCLAD is contraindicated in patients with active or latent tuberculosis. All patients must be evaluated for both active and inactive ("latent") tuberculosis infection, according to local guidelines (see WARNINGS AND PRECAUTIONS, Immune).
- All patients must be evaluated for hepatitis B and C virus (HBV and HCV) (see WARNINGS AND PRECAUTIONS, Immune).
- Immunization should be completed at least 6 weeks prior to treatment with MAVENCLAD (see WARNINGS AND PRECAUTIONS, Immune, Vaccination).
- Check varicella-zoster (VZV) antibody status before starting therapy if there is no health care professional confirmed history of chicken pox or vaccination with varicella vaccine; if negative, vaccination is recommended, with a delay in treatment initiation with MAVENCLAD for 6 weeks following vaccination (see WARNINGS AND PRECAUTIONS, Immune, Vaccination).

- In patients who have previously been treated with immunomodulating or immunosuppressive medicinal products, MAVENCLAD must only be initiated if lymphocyte counts have been found to be normal (see WARNINGS AND PRECAUTIONS, Hematologic; DOSAGE AND ADMINISTRATION).
- When switching from an MS agent with a risk of progressive multifocal leukoencephalopathy (PML), a baseline magnetic resonance imaging (MRI) is recommended (see WARNINGS AND PRECAUTIONS, Immune, Progressive Multifocal Leukoencephalopathy).
- Pregnancy must be excluded (see WARNINGS AND PRECAUTIONS, Sexual Function/Reproduction).
- Women of childbearing potential and males who could potentially father a child should be counselled on the potential for serious risk to the fetus and the need for effective contraception during MAVENCLAD treatment and for at least 6 months after the last dose (see WARNINGS AND PRECAUTIONS, Sexual Function/Reproduction).

<u>During treatment with MAVENCLAD and following treatment discontinuation:</u>

- Instruct patients to promptly report symptoms of infection during treatment and following discontinuation of MAVENCLAD (see WARNINGS AND PRECAUTIONS, Immune).
- Lymphocyte counts must be determined:
    - before initiating MAVENCLAD in year 1,
    - before initiating MAVENCLAD in year 2, and
    - periodically between treatment courses and thereafter. Should lymphocyte counts drop below 500 cells/mm³ (CTCAE v4.0 Grade 3 toxicity), active monitoring is recommended until values increase above 500 cells/mm³.

  See WARNINGS AND PRECAUTIONS, Hematologic and DOSAGE AND ADMINISTRATION.

**Neoplasms**

The actions of cladribine yield DNA damage (see TOXICOLOGY). Due to the known genotoxicity of cladribine and immunosuppression associated with the use of nucleoside analogues like MAVENCLAD, MAVENCLAD could potentially increase the risk of malignancies.

In clinical trials, events of malignancies were observed more frequently in cladribine-treated patients compared to patients who received placebo (see ADVERSE REACTIONS, Neoplasms).

MAVENCLAD is contraindicated in MS patients with active malignancies (see CONTRAINDICATIONS). Patients with prior malignancy were excluded from participating in the clinical development program; therefore, an individual benefit-risk evaluation should be performed before initiating MAVENCLAD in patients with prior malignancy. Patients treated with MAVENCLAD should be advised to follow standard cancer screening guidelines.

Cladribine was clastogenic in nonclinical *in vitro* and *in vivo* studies, but not mutagenic in bacterial and mammalian cell assays and did not cause any tumors of clinical significance in mice (see TOXICOLOGY).

**Hematologic**
Cladribine's mode of action is closely linked to a reduction in lymphocyte count. The effect on lymphocyte count is dose-dependent and may persist for some time after cladribine elimination from the body upon cessation of dosing (see DOSAGE AND ADMINISTRATION; ADVERSE REACTIONS; ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics). Decreases in neutrophil count, red blood cell count, hematocrit, hemoglobin or platelet count compared to baseline values have also been observed in clinical studies, although these parameters usually remain within normal limits. A complete blood count (CBC) is recommended prior to initiating treatment with MAVENCLAD and monitoring lymphocyte counts is recommended after initiating treatment with MAVENCLAD (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

Additive hematological adverse reactions may be expected if MAVENCLAD is administered concomitantly with other substances that affect the hematological profile (see DRUG INTERACTIONS, Hematotoxic, immunomodulating or immunosuppressive agents).

In patients who require blood transfusion, irradiation of cellular blood components is recommended prior to administration to prevent transfusion-related graft-versus-host disease. Consultation with a hematologist is advised.

**Immune**

Infections
Cladribine can reduce the body's immune defence and increase the likelihood of infections, including opportunistic infections, especially in patients who develop severe lymphopenia. The risk of infection may persist until recovery of lymphopenia after completion of treatment (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics). Latent infections may be activated, including tuberculosis or hepatitis (see CONTRAINDICATIONS). During the clinical development program, 3 cases of tuberculosis were reported, including 1 fatal case (see ADVERSE REACTIONS, Infections). Therefore, screening for latent infections is recommended prior to initiation of therapy in year 1 and year 2. A delay in initiation of MAVENCLAD is recommended until the infection is adequately treated. Patients should be advised about the potential for increased risk of infections and necessary vigilance during treatment and after discontinuation of treatment with MAVENCLAD. In the two placebo-controlled Phase III studies in MS in which MAVENCLAD was used as monotherapy at a cumulative dose of 3.5 mg/kg, the overall rate of infections and serious infections with MAVENCLAD was slightly higher than that of placebo (see ADVERSE REACTIONS, Infections).

MAVENCLAD is contraindicated in patients at an increased risk of opportunistic infections and in patients with active infections, including active chronic bacterial, fungal or viral infections (see CONTRAINDICATIONS).

A delay in initiation of MAVENCLAD should also be considered in patients with an acute infection until the infection is fully controlled.

*Herpetic infections*
Physicians should advise patients about the potential for increased risk of infections, in particular herpes zoster (shingles), and necessary vigilance during treatment and after discontinuation of treatment with MAVENCLAD. Reports of herpes infections were common in patients treated with MAVENCLAD. Herpes zoster infections occurred mainly in the cladribine treatment group and were dermatomal in nature (see ADVERSE REACTIONS, Infections). For patients who develop serious infections, the benefits and risks of treatment should be re-assessed prior to re-initiation of treatment.

The frequency of herpes zoster infections was increased in patients with Grade 3 and Grade 4 lymphopenia (see ADVERSE REACTIONS). Patients with lymphocyte counts below 500 cells/$mm^3$ should be actively monitored for signs and symptoms suggestive of infection. If lymphocyte counts drop below 200 cells/$mm^3$, anti-herpes prophylaxis according to local standard practice should be considered during the time of Grade 4 lymphopenia. Treatment of herpes zoster should follow current relevant guidelines.

*Progressive Multifocal Leukoencephalopathy (PML)*
In the clinical trial data base (1976 patients, 8650 patient years) no case of PML has been reported. However, a baseline MRI should be considered before initiating MAVENCLAD. This is particularly recommended if patients are switched from other MS agents that have a risk of PML. Cases of PML have been reported in the post-market setting in patients treated with parenteral cladribine for non-MS diseases with a different treatment regimen. PML is an opportunistic infection caused by JC virus (JCV) that typically only occurs in patients who are immunocompromised, which may be fatal or result in severe disability. Physicians should be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. If PML is suspected, MAVENCLAD treatment should not be re-initiated until PML has been excluded. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

Vaccination
Treatment with MAVENCLAD must not be initiated within 6 weeks after vaccination with live or attenuated live vaccines because of a risk of active vaccine infection. Also patients must not be vaccinated with live or attenuated live vaccines during MAVENCLAD treatment and also not after MAVENCLAD treatment as long as the patient's white blood cell counts are not within normal limits.

Particular attention is recommended for patients who have no history of exposure to varicella zoster virus. Varicella (chickenpox) vaccination of antibody-negative patients is recommended prior to initiation of MAVENCLAD therapy. Initiation of treatment with MAVENCLAD must be postponed for 6 weeks to allow for the full effect of vaccination to occur.

**Switching to or from MAVENCLAD treatment**
In patients who have previously been treated with immunomodulating or immunosuppressive medicinal products, MAVENCLAD must only be initiated if lymphocyte counts have been found to be normal (see DOSAGE AND ADMINISTRATION, Dosing Considerations). Subsequent use of such products after treatment with MAVENCLAD may lead to an additive effect on the immune system and caution is therefore indicated.

**Sexual Function/Reproduction**
Contraception in males and females: In women of childbearing potential, pregnancy must be excluded before the initiation of MAVENCLAD in year 1 and year 2, and prevented by use of effective contraception during MAVENCLAD treatment and for at least 6 months after the last dose (see DRUG INTERACTIONS, Hormonal contraceptives). Women who become pregnant under therapy with MAVENCLAD should discontinue treatment.

Taking into account the potential genotoxic effect of cladribine on spermatozoa, male-mediated developmental toxicity cannot be ruled out. Cladribine caused testicular degenerative changes in mice and in one male monkey in a s.c. chronic study. Therefore, male patients must take precautions to prevent pregnancy of their partner during MAVENCLAD treatment and for at least 6 months after the last dose. The effect of cladribine on male human fertility is unknown.

If a female patient or the female partner of a male patient become pregnant during MAVENCLAD therapy or within 6 months after the last dose, it is recommended that they be informed about the potential hazard to the fetus.

**Special Populations**
Pregnant Women: There is limited data from pregnant women exposed to MAVENCLAD prior to conception. MAVENCLAD is contraindicated in pregnant women (see CONTRAINDICATIONS).

Pregnancy must be excluded before initiating treatment in year 1 and year 2 and prevented by use of effective contraception during MAVENCLAD treatment and for at least 6 months after the last dose.

Cladribine has been shown to inhibit DNA synthesis and other active substances that inhibit DNA synthesis (e.g. methotrexate) have been reported to be teratogenic in humans. Therefore, cladribine may increase the risk of congenital malformations when administered during pregnancy (see TOXICOLOGY, Reproductive toxicity).

Studies in animals have shown reproductive toxicity (see TOXICOLOGY, Reproductive toxicity).

Nursing Women: It is not known whether cladribine is excreted in human milk. A risk to the newborns/infants cannot be excluded. MAVENCLAD is contraindicated in nursing women (see CONTRAINDICATIONS).

Pediatrics (< 18 years of age): The safety and efficacy of MAVENCLAD in patients below the age of 18 years have not been studied.

Geriatrics (> 65 years of age): Clinical studies of MAVENCLAD in MS did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Caution is recommended when MAVENCLAD is used in elderly patients, taking into account the potential greater frequency of decreased hepatic or renal function, concomitant diseases and other medicinal therapies.

Renal Impairment: No dedicated studies have been conducted in patients with renal impairment. In patients with mild renal impairment (creatinine clearance 60 to 89 mL/min), no dosage adjustment is considered necessary.

In patients with moderate or severe renal impairment (creatinine clearance < 60 mL/min), a decrease in cladribine clearance can be predicted (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Excretion). Safety and efficacy in patients with moderate or severe renal impairment have not been established. Therefore, MAVENCLAD is contraindicated in these patients (see CONTRAINDICATIONS).

Hepatic Impairment: No studies have been conducted in patients with hepatic impairment. Although the importance of hepatic function for the elimination of cladribine is considered negligible (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Metabolism), in the absence of data, use of MAVENCLAD is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh score > 6) (see DOSAGE AND ADMINISTRATION, Hepatic Impairment).

Fructose Intolerance: MAVENCLAD contains sorbitol. Patients with hereditary problems of fructose intolerance should not take this medicinal product.

**Monitoring and Laboratory Tests**
Lymphocyte counts must be determined:

- before initiating MAVENCLAD in year 1,
- before initiating MAVENCLAD in year 2, and
- periodically between treatment courses and thereafter.

For treatment decisions based on the patient's lymphocyte counts, see DOSAGE AND ADMINISTRATION, Dosing Considerations and WARNINGS AND PRECAUTIONS, General and Immune.

## ADVERSE REACTIONS

### Adverse Drug Reaction Overview

The most clinically relevant adverse reactions reported in MS patients who received MAVENCLAD at the recommended cumulative dose of 3.5 mg/kg over 2 years in clinical studies were lymphopenia and herpes zoster. The incidence of herpes zoster was higher during the period of Grade 3 (< 500 to 200 cells/mm³) or 4 (< 200 cells/mm³) lymphopenia compared to the time when the patients were not experiencing Grade 3 or 4 lymphopenia (see WARNINGS AND PRECAUTIONS, Immune, Herpetic infections).

### Clinical Trial Adverse Drug Reactions

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Table 1 presents treatment-emergent adverse events derived from pooled data from two placebo-controlled Phase III studies in MS in which MAVENCLAD was used as monotherapy at a cumulative dose of 3.5 mg/kg. The safety database from these studies comprises 1303 patients.

**Table 1 Treatment-emergent adverse events in two placebo-controlled studies (occurring in ≥ 1% of patients and reported for MAVENCLAD 3.5 mg/kg at ≥ 1% higher rate than placebo)**

| **System Organ Class**<br>Preferred Term | **Cladribine 3.5 mg/kg cumulative dose**<br>**n=662**<br>**n (%)** | **Placebo**<br>**n=641**<br>**n (%)** |
|---|---|---|
| **Blood and lymphatic system disorders** | | |
| Lymphopenia*[1] | 132 (19.9) | 8 (1.2) |
| Leukopenia | 26 (3.9) | 3 (0.5) |
| Decrease in neutrophil count*[2] | 18 (2.7) | 5 (0.8) |
| **Gastrointestinal disorders** | | |
| Nausea | 70 (10.6) | 58 (9.0) |
| Abdominal pain upper | 34 (5.1) | 21 (3.3) |
| Toothache | 27 (4.1) | 20 (3.1) |
| **General disorders and administration site conditions** | | |
| Influenza like illness | 45 (6.8) | 37 (5.8) |
| Pyrexia | 23 (3.5) | 16 (2.5) |
| **Infections and infestations** | | |
| Upper respiratory tract infection | 74 (11.2) | 58 (9.0) |
| Influenza | 49 (7.4) | 40 (6.2) |
| Bronchitis | 29 (4.4) | 19 (3.0) |
| Oral herpes* | 17 (2.6) | 9 (1.4) |

| System Organ Class<br>Preferred Term | Cladribine 3.5 mg/kg cumulative dose<br>n=662<br>n (%) | Placebo<br><br>n=641<br>n (%) |
|---|---|---|
| Viral upper respiratory tract infection | 17 (2.6) | 6 (0.9) |
| Respiratory tract infection viral | 16 (2.4) | 9 (1.4) |
| Gastroenteritis | 16 (2.4) | 8 (1.2) |
| Herpes zoster* | 13 (2.0) | 1 (0.2) |
| Vaginal infection | 9 (1.4) | 1 (0.2) |
| **Musculoskeletal And Connective Tissue Disorders** | | |
| Back pain | 50 (7.6) | 41 (6.4) |
| **Nervous system disorders** | | |
| Headache | 171 (25.8) | 134 (20.9) |
| **Psychiatric disorders** | | |
| Anxiety | 22 (3.3) | 12 (1.9) |
| **Skin and subcutaneous tissue disorders** | | |
| Alopecia* | 18 (2.7) | 8 (1.2) |
| Dermatitis allergic | 16 (2.4) | 3 (0.5) |
| Rash* | 15 (2.3) | 8 (1.2) |

n = number of patients

* term considered adverse reactions (i.e. reasonably associated with the use of oral cladribine)

[1] includes terms lymphopenia, lymphocyte count decreased and lymphocyte count abnormal

[2] includes terms neutropenia and neutrophil count decreased

**Abnormal Hematologic and Clinical Chemistry Findings**

In clinical studies, 20% to 25% of the patients treated with a cumulative dose of MAVENCLAD 3.5 mg/kg over 2 years as monotherapy developed transient Grade 3 or 4 lymphopenia compared to 0.5% in patients on placebo. Grade 4 lymphopenia was seen in less than 1% of the patients treated with cladribine compared to none in patients on placebo. The largest proportion of patients with Grade 3 or 4 lymphopenia was seen 2 months after the first cladribine dose in each year (4.0% and 11.3% of patients with Grade 3 lymphopenia in year 1 and year 2, 0% and 0.4% of patients with Grade 4 lymphopenia in year 1 and year 2) (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics). 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 MAVENCLAD treatment (see WARNINGS AND PRECAUTIONS, Hematologic) and criteria for initiating and continuing MAVENCLAD treatment must be followed (see DOSAGE AND ADMINISTRATION, Dosing Considerations).

**Neoplasms**
In pooled data from two placebo-controlled, 2-year monotherapy Phase III clinical studies, events of malignancy were reported in 5/662 (0.76%) patients receiving cladribine at a cumulative dose of 3.5 mg/kg and in 0/641 (0%) patients on placebo; the malignant events included malignant melanoma, ovarian cancer, metastatic pancreatic carcinoma, papillary thyroid cancer, and squamous cell carcinoma of skin.

Overall in clinical studies and long-term follow-up of patients treated with a cumulative dose of 3.5 mg/kg oral cladribine, similar incidences of malignant events were observed. Additional events during long-term follow-up in patients treated with cladribine were malignant melanoma, breast cancer, rectal cancer, bile duct cancer, and basal cell carcinoma.

**Infections**
In the two placebo-controlled Phase III studies in MS in which oral cladribine was used as monotherapy at a cumulative dose of 3.5 mg/kg, slightly higher rates of infections in general (49.5% in cladribine-treated patients compared to 44.1% in patients on placebo) and serious infections (1.8% in cladribine treated patients compared to 1.1% in patient on placebo) were observed.

Apart from oral herpes and dermatomal herpes zoster (see Table 1 above) only tuberculosis was considered causally related to cladribine treatment. Three cases of tuberculosis (including 1 fatal case) have been observed in the clinical program, which were all reported prior to the implementation of mandatory pre-screening for tuberculosis.

For recommendations regarding screening for infections and other preventive measures, see WARNINGS AND PRECAUTIONS, General and Immune.

**CLARITY EXT**
Patients who had completed the CLARITY study (see CLINICAL TRIALS) could be enrolled in CLARITY EXT. In this extension study, 806 patients received either placebo or a cumulative dose of cladribine 3.5 mg/kg (in a regimen similar to that used in CLARITY) over a 96-week study period. The primary objective of this study was safety, while efficacy endpoints were exploratory. The safety outcomes were consistent with the safety profile observed for the previous CLARITY study.

## DRUG INTERACTIONS

**Overview**
MAVENCLAD contains hydroxypropyl betadex which may be available for complex formation with other agents, potentially leading to an increase in bioavailability of such a product (see DETAILED PHARMACOLOGY, Pharmacokinetic interactions).

Potent inhibitors of concentrative nucleoside transporters (CNT) or equilibrative nucleoside transporters (ENT) and Breast Cancer Resistance Protein (BCRP) transporter inhibitors may theoretically alter the bioavailability, intracellular distribution and renal elimination of cladribine; the clinical relevance of these findings is unknown (see DETAILED PHARMACOLOGY, Pharmacokinetic interactions).

No clinically relevant interaction of cladribine is expected with the cytochrome P450 (CYP) enzyme system or with inhibitors or inducers of the P-glycoprotein (MDR1). The effects of inducers of the efflux transporter BCRP on the bioavailability and disposition of cladribine have not been formally studied (see DETAILED PHARMACOLOGY, Pharmacokinetic interactions).

**Drug-Drug Interactions**
Because of the hydroxypropyl betadex component in MAVENCLAD, it is recommended that administration of any other oral medicinal product be separated from that of MAVENCLAD by at least 3 hours during the limited number of days of cladribine administration.

Hematotoxic, immunomodulating or immunosuppressive agents
Use of MAVENCLAD in immunocompromised patients, including patients receiving immunosuppressive, immunomodulating or myelosuppressive therapies with, e.g., methotrexate, cyclophosphamide, cyclosporine or azathioprine, or chronic use of corticosteroids is contraindicated because of a risk of additive effects on the immune system (see CONTRAINDICATIONS).

Acute short-term therapy with corticosteroids can be administered during MAVENCLAD treatment.

Because of the cladribine-induced reduction in lymphocyte count, additive hematological adverse reactions may be expected if MAVENCLAD is administered concomitantly with other substances that affect the hematological profile (e.g. carbamazepine). Careful monitoring of hematological parameters is recommended in such cases.

In clinical studies, when interferon-beta was used in combination with cladribine, a more pronounced effect in the reduction of lymphocyte count was observed.

Live or live attenuated vaccines
Treatment with MAVENCLAD must not be initiated within 6 weeks after vaccination with live or attenuated live vaccines because of a risk of active vaccine infection. Also patients must not be vaccinated with live or attenuated live vaccines during MAVENCLAD treatment and also not after MAVENCLAD treatment as long as the patient's white blood cell counts are not within normal limits.

Nucleoside transporter and BCRP inhibitors
It is recommended that co-administration of potent ENT, CNT or BCRP transporter inhibitors be avoided during the 4- to 5-day MAVENCLAD treatment. Known inhibitors of nucleoside transporters include dilazep, dipyridamole, nifedipine, nimodipine, cilostazol, sulindac and reserpine. Known BCRP inhibitors include cyclosporine, gefitinib, imatinib, reverse transcriptase inhibitors, other antivirals (e.g., elvitegravir, cobicistat) and eltrombopag.

If this is not possible, selection of alternative concomitant medicinal products with no, or minimal transporter inhibiting properties should be considered. If this is not possible, dose reduction to the minimum mandatory dose of medicinal products containing these compounds, separation in the timing of administration and careful patient monitoring is recommended.

Potent BCRP transporter inducers
The effects of inducers of the efflux transporter BCRP on the bioavailability and disposition of cladribine have not been formally studied. A possible decrease in cladribine exposure should be considered if potent BCRP transporter inducers (e.g. chronic use of corticosteroids) are co-administered.

Hormonal contraceptives
No interaction studies have been performed with oral contraceptives. Thus, it is not known whether cladribine may reduce the effectiveness of systemically acting hormonal contraceptives. Women using hormonal contraceptives should add a barrier method during MAVENCLAD treatment and for at least 4 weeks after the last dose in each treatment year.

**Drug-Food Interactions**
It is unlikely that food intake will have a clinically relevant effect on the extent of absorption. Therefore, the tablets can be taken independent of food intake (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption).

**Drug-Herb Interactions**
Interactions with herbal products have not been studied.

**Drug-Laboratory Interactions**
Interactions with laboratory tests have not been studied.

## DOSAGE AND ADMINISTRATION

Treatment with MAVENCLAD must be initiated and supervised by a neurologist experienced in the treatment of MS.

### Dosing Considerations

Criteria for initiating and continuing therapy
Lymphocyte counts must be:

- normal before initiating MAVENCLAD in year 1,
- at least 800 cells/mm³ (i.e., Grade 0 or 1) before initiating MAVENCLAD in year 2.

See WARNINGS AND PRECAUTIONS, General.

If necessary, the treatment course in year 2 can be delayed for up to 6 months to allow for recovery of lymphocytes. If this recovery takes more than 6 months, the patient should not receive MAVENCLAD anymore.

Concomitant use of other oral medications
It is recommended that administration of any other oral medicinal product be separated from that of MAVENCLAD by at least 3 hours during the limited number of days of MAVENCLAD administration (see DRUG INTERACTIONS, Drug-Drug Interactions).

### Recommended Dose and Dosage Adjustment

The recommended cumulative dose of MAVENCLAD is 3.5 mg/kg body weight over 2 years, administered as 1 treatment course of 1.75 mg/kg per year, followed by observation for another 2 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. Each treatment week consists of 4 or 5 days on which a patient receives 10 mg or 20 mg (one or two tablets) as a single daily dose, depending on body weight.

The efficacy of MAVENCLAD for treatment duration beyond 2 years has not been established (see INDICATIONS AND CLINICAL USE). Therefore, no further dosing recommendation can be provided beyond two treatment courses.

Distribution of dose
The distribution of the total dose over the 2 years of treatment is provided in Table 2. Note that for some weight ranges the number of tablets may vary from one treatment week to the next. Use of oral cladribine in patients weighing less than 40 kg has not been investigated.

**Table 2 Dose of MAVENCLAD per year and treatment week by patient weight**

| Weight range | Dose in mg (number of 10 mg tablets) per week | | | |
|---|---|---|---|---|
| | Year 1 treatment course | | Year 2 treatment course | |
| kg | Treatment week 1 | Treatment week 2 | Treatment week 1 | Treatment week 2 |
| 40 to < 50 | 40 mg (4 tablets) | 40 mg (4 tablets) | 40 mg (4 tablets) | 40 mg (4 tablets) |
| 50 to < 60 | 50 mg (5 tablets) | 50 mg (5 tablets) | 50 mg (5 tablets) | 50 mg (5 tablets) |
| 60 to < 70 | 60 mg (6 tablets) | 60 mg (6 tablets) | 60 mg (6 tablets) | 60 mg (6 tablets) |
| 70 to < 80 | 70 mg (7 tablets) | 70 mg (7 tablets) | 70 mg (7 tablets) | 70 mg (7 tablets) |
| 80 to < 90 | 80 mg (8 tablets) | 70 mg (7 tablets) | 80 mg (8 tablets) | 70 mg (7 tablets) |
| 90 to < 100 | 90 mg (9 tablets) | 80 mg (8 tablets) | 90 mg (9 tablets) | 80 mg (8 tablets) |
| 100 to < 110 | 100 mg (10 tablets) | 90 mg (9 tablets) | 100 mg (10 tablets) | 90 mg (9 tablets) |
| 110 and above | 100 mg (10 tablets) | 100 mg (10 tablets) | 100 mg (10 tablets) | 100 mg (10 tablets) |

Table 3 shows how the total number of tablets per treatment week is distributed over the individual days. It is recommended that the daily MAVENCLAD doses in each treatment week be taken at intervals of 24 hours at approximately the same time each day. If a daily dose consists of two tablets, both tablets are taken together as a single dose.

**Table 3 MAVENCLAD 10 mg tablets per week day**

| Total number of 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 |

Renal Impairment

No dedicated studies have been conducted in patients with renal impairment.

In patients with mild renal impairment (creatinine clearance 60 to 89 mL/min), no dosage adjustment is considered necessary.

Safety and efficacy in patients with moderate or severe renal impairment (creatinine clearance < 60 mL/min) have not been established. Therefore, MAVENCLAD is contraindicated in these patients (see CONTRAINDICATIONS).

Hepatic Impairment
No studies have been conducted in patients with hepatic impairment.

Although the importance of hepatic function for the elimination of cladribine is considered negligible (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Metabolism), in the absence of data, use of MAVENCLAD is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh score > 6).

Geriatrics (> 65 years of age)
Clinical studies with oral cladribine in MS did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

Caution is recommended when MAVENCLAD is used in elderly patients, taking into account the potential greater frequency of decreased hepatic or renal function, concomitant diseases and other medicinal therapies.

Pediatrics (< 18 years of age)
The safety and efficacy of MAVENCLAD in patients below the age of 18 years have not been studied.

**Missed Dose**
A missed dose must be taken as soon as remembered on the same day according to the treatment schedule.

A missed dose must not be taken together with the next scheduled dose on the following day. In the case of a missed dose, the patient must take the missed dose on the following day, and extend the number of days in that treatment week. For example, if a patient forgets to take the Day 3 dose and does not remember until Day 4, the Day 3 dose is taken on Day 4, and the total number of days in the treatment week is extended by one day. If two consecutive doses are missed, the same rule applies, and the number of days in the treatment week is extended by two days.

**Administration**
MAVENCLAD is taken orally and swallowed without chewing. It should be taken with water, with or without food.

As the tablets are uncoated, they must be swallowed immediately once removed from the blister and not be left exposed on surfaces or handled for any period of time greater than that required for dosing. If a tablet is left on a surface, or if a broken or fragmented tablet is released from the blister, the area must be thoroughly washed.

The patient's hands must be dry when handling the tablets and washed thoroughly afterwards.

## OVERDOSAGE

There is limited experience with overdose of oral cladribine. Lymphopenia is known to be dose-dependent (see WARNINGS AND PRECAUTIONS, Hematologic; ADVERSE REACTIONS).

There is no known specific antidote to an overdose of MAVENCLAD. Treatment consists of careful observation and initiation of appropriate supportive measures. Discontinuation of MAVENCLAD may need to be considered. Because of the extensive intracellular and tissue distribution, hemodialysis is unlikely to eliminate cladribine to a significant extent.

Particularly close monitoring of hematological parameters is recommended in patients who have been exposed to an overdose of cladribine.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

Cladribine (2-chlorodeoxyadenosine) is a nucleoside analogue of deoxyadenosine. A chlorine substitution at position 2 in the purine ring decreases the degradation of cladribine by adenosine deaminase, increasing the intracellular residence time of the cladribine prodrug. Subsequent phosphorylation of cladribine by deoxycytidine kinase (DCK) and nucleoside kinases to its active triphosphate form, 2-chlorodeoxyadenosine triphosphate (Cd-ATP), is particularly efficiently achieved in T and B lymphocytes, due to their constitutively high DCK and relatively low 5'-nucleotidase (5'-NTase) levels. A high DCK to 5'-NTase ratio favours the accumulation of toxic levels of Cd-ATP intracellularly, making non-dividing and dividing lymphocytes particularly susceptible to cell death through the induction of apoptosis or inhibition of DNA synthesis.

Variations in the expression levels of DCK and 5′-NTases between immune cell subtypes may explain differences in immune cell sensitivity to cladribine. Because of these expression levels, cells of the innate immune system are less affected than cells of the adaptive immune system.

MS pathology involves a complex chain of events in which different immune cell types, including autoreactive T and B cells play a key role. The mechanism by which cladribine exerts its therapeutic effects in MS is not fully elucidated but its predominant effect on lymphocytes is thought to interrupt the cascade of immune events central to MS.

### Pharmacodynamics

Cladribine has been shown to exert long-lasting effects by preferentially targeting lymphocytes and the autoimmune processes involved in the pathophysiology of MS.

Across studies, the largest proportion of patients with Grade 3 or 4 lymphopenia (< 500 to 200 cells/mm³ or < 200 cells/mm³) was seen 2 months after the first cladribine dose in each year, indicating a time gap between cladribine plasma concentrations and the maximum hematological effect.

Across clinical studies, data with the proposed cumulative dose of 3.5 mg/kg body weight show a gradual improvement in the median lymphocyte counts back to the normal range at week 84 from the first dose of cladribine (approximately 30 weeks after the last dose of cladribine). The lymphocyte counts of more than 75% of patients returned to the normal range by week 144 from the first dose of cladribine (approximately 90 weeks after the last dose of cladribine).

Treatment with oral cladribine leads to rapid, sustained reductions in circulating CD4+ and CD8+ T cells. CD8+ T cells have a less pronounced decrease and a faster recovery than CD4+ T cells, resulting in a temporarily decreased CD4 to CD8 ratio. Cladribine reduces CD19+ B cells and CD16+/CD56+ natural killer cells, which also recover faster than CD4+ T cells.

**Pharmacokinetics**
Cladribine is a prodrug that has to be phosphorylated intracellularly to become biologically active. Cladribine pharmacokinetics were studied in MS patients and patients with malignancies, and in *in vitro* systems.

**Table 4 Summary of cladribine pharmacokinetic parameters in patients with MS or malignancies**

| | $C_{max}$ | $t_{½}$ | $AUC_{0-\infty}$ | Clearance | Volume of distribution |
|---|---|---|---|---|---|
| **Means, range or population estimates** | 22 to 29 ng/mL | 23 h | 80 to 101 ng·h/mL | 45.6 L/h | 480 to 490 L |

Absorption: Following oral administration, cladribine is rapidly absorbed. Administration of 10 mg cladribine resulted in a cladribine mean $C_{max}$ in the range of 22 to 29 ng/mL and corresponding mean AUC in the range of 80 to 101 ng•h/mL (arithmetic means from various studies).

When oral cladribine was given in fasted state, median $T_{max}$ was 0.5 h (range 0.5 to 1.5 h). When administered with a high-fat meal, cladribine absorption was delayed (median $T_{max}$ 1.5 h, range 1 to 3 h) and $C_{max}$ was reduced by 29% (based on geometric mean), while AUC was essentially unchanged. The bioavailability of 10 mg oral cladribine was approximately 40%.

Distribution: The volume of distribution is large, indicating extensive tissue distribution and intracellular uptake. Studies revealed a mean volume of distribution of cladribine in the range of 480 to 490 L. The plasma protein binding of cladribine is 20%, and independent of plasma concentration.

Cladribine has the potential to penetrate the blood brain barrier. A small study in cancer patients has shown a cerebrospinal fluid/plasma concentration ratio of approximately 0.25.

Cladribine and/or its phosphorylated metabolites are substantially accumulated and retained in human lymphocytes. Intra- versus extracellular accumulation ratios were found to be around 30 to 40 already 1 hour after cladribine exposure.

Metabolism: The metabolism of cladribine was studied in MS patients following the administration of a single 10 mg tablet and a single 3 mg intravenous dose. Following both oral and intravenous administration, the parent compound cladribine was the main component present in plasma and urine. The primary metabolite 2-chloroadenine proved to be a minor metabolite both in plasma and in urine, e.g. accounting only for ≤ 3% of plasma parent drug exposure after oral administration. Only traces of other metabolites could be found in plasma and in urine.

In hepatic *in vitro* systems, negligible metabolism of cladribine was observed (at least 90% was unchanged cladribine). *In vitro* studies also showed negligible transporter-mediated uptake of cladribine into human hepatocytes.

After entering the target cells, cladribine is phosphorylated to cladribine monophosphate (Cd-AMP) by nucleoside kinases including DCK. Cd-AMP is further phosphorylated to cladribine diphosphate (Cd-ADP) and cladribine triphosphate (Cd-ATP). The dephosphorylation and deactivation of Cd-AMP is catalysed by cytoplasmic 5´-NTase.

Intracellular half-life of Cd-AMP was 15 h. Intracellular half-life of Cd-ATP was 10 h and the plasma half-life was 21 h.

Excretion: Based on pooled population pharmacokinetic data from various studies, the median values were 22.2 L/h for renal clearance and 23.4 L/h for non-renal clearance. Renal clearance exceeded the glomerular filtration rate, indicating active renal tubular secretion of cladribine.

The estimated terminal half-life for a typical patient from the population pharmacokinetic analysis is approximately 1 day. This however does not result in any drug accumulation after once daily dosing as this half-life only accounts for a small portion of the AUC.

Dose and time dependence
After oral administration of cladribine across a dose range from 3 to 20 mg, $C_{max}$ and AUC increased in a dose-proportional fashion, suggesting that absorption is not affected by rate- or capacity-limited processes up to a 20 mg oral dose.

No significant accumulation of cladribine concentration in plasma has been observed after repeated dosing. There is no indication that cladribine pharmacokinetics might change in a time-dependent fashion after repeated administration.

Special populations and conditions
No studies have been conducted to evaluate the pharmacokinetics of cladribine in elderly or in pediatric MS patients, or in subjects with renal or hepatic impairment. A population pharmacokinetic analysis did not show any effect of age (range 18 to 65 years) on cladribine pharmacokinetics.

Gender: A population pharmacokinetic analysis did not show any effect of gender on cladribine pharmacokinetics.

Hepatic Insufficiency: The role of hepatic function for the elimination of cladribine is considered negligible.

Renal Insufficiency: Renal clearance of cladribine was shown to be dependent on creatinine clearance. Based on a population pharmacokinetic analysis including patients with normal renal function and with mild renal impairment, total clearance in patients with mild renal impairment ($CL_{CR}$ = 65 mL/min) is estimated to decrease by 18%. The predicted decrease in cladribine clearance is 30% in patients with moderate renal impairment ($CL_{CR}$ = 40 mL/min) and 40% in patients with severe renal impairment ($CL_{CR}$ = 20 mL/min).

## STORAGE AND STABILITY

Store MAVENCLAD at room temperature (15°C to 30°C).

Store in the original package in order to protect from moisture.

## SPECIAL HANDLING INSTRUCTIONS

The patient's hands must be dry when handling the tablets and washed thoroughly afterwards.

As tablets are uncoated, they must be swallowed immediately once removed from the blister and not be left exposed on surfaces or handled for any period of time greater than that required for dosing. If a tablet is left on a surface, or if a broken or fragmented tablet is released from the blister, the area must be thoroughly washed.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

MAVENCLAD is available as tablets containing 10 mg of cladribine: white, round, biconvex tablets, engraved with 'C' on one side and '10' on the other side.

Nonmedicinal ingredients: hydroxypropyl betadex, sorbitol and magnesium stearate.

MAVENCLAD is supplied in an aluminum-aluminum blister which is sealed in a cardboard wallet and fixed in a child-resistant carton.

Pack sizes of 1, 4, 5, 6, 7 or 8 tablets. Not all pack sizes may be marketed.

## PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

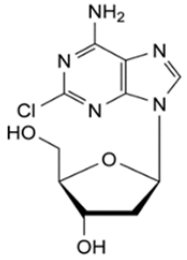
### Drug Substance

Proper name: Cladribine (2-chlorodeoxyadenosine)

Chemical name: (2R,3S,5R)-5-(6-amino-2-chloropurin-9-yl)-2-(hydroxymethyl)oxolan-3-ol (IUPAC)
2-chloro-2'-deoxyadenosine (USP)
2-chloro-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)-9*H*-purin-6-amine (Ph. Eur.)

Molecular formula and molecular mass: $C_{10}H_{12}ClN_5O_3$
285.7

Structural formula:




Physiochemical properties: White to almost white powder; solubility between 6.3 mg/mL and 4.4 mg/mL over the pH range of 1.0 - 7.5.

## CLINICAL TRIALS

The efficacy and safety of MAVENCLAD (cladribine) in the treatment of RRMS was demonstrated in a Phase III, placebo-controlled study.

### Study demographics and trial design

**Table 5 Summary of patient demographics for MAVENCLAD in RRMS**

| Study | Trial design | Dosage, route of administration and duration | Study subjects (n = number) | Mean age (Range) | Gender |
|---|---|---|---|---|---|
| CLARITY (Study 25643) | Phase III, randomized, double-blind, three-arm, placebo-controlled, multi-center study in patients with RRMS | Cladribine 3.5 mg/kg, cladribine 5.25 mg/kg or placebo randomized 1:1:1 ratio administered as 2 treatment courses separated by 1 year | Cladribine 3.5 mg/kg: n=433 Cladribine 5.25 mg/kg: n=456 Placebo: n=437 | 3.5 mg/kg: 37.9 years 5.25 mg/kg: 39.1 years Placebo: 38.7 years Range: 18 - 65 years | F: 898 M: 428 |

CLARITY was a Phase III, randomized, double-blind, 3-arm, placebo-controlled, multicenter study to evaluate the safety and efficacy of MAVENCLAD in patients with RRMS.

A total of 1326 patients were equally randomized into three treatment groups. Patients received either placebo, or a cumulative dose of cladribine of 3.5 mg/kg or 5.25 mg/kg body weight over the 96-week (2-year) study period in 2 treatment courses. Patients randomised to the 3.5 mg/kg cumulative dose received a first treatment course at weeks 1 and 5 of the first year and a second treatment course at weeks 1 and 5 of the second year. Patients randomised to the 5.25 mg/kg cumulative dose received additional treatment at weeks 9 and 13 of the first year. Cladribine was administered orally as 10 mg tablets, with the number of tablets taken daily based on the patient's body weight using 10 kg weight ranges (see DOSAGE AND ADMINISTRATION).

The majority of patients in the placebo (87.0%) and the cladribine 3.5 mg/kg (91.9%) and 5.25 mg/kg (89.0%) treatment groups completed the full 96 weeks of the study. The mean age ranged from 37.9 years in the cladribine 3.5 mg/kg group to 39.1 years in the cladribine 5.25 mg/kg group. Most (> 97%) patients were white, and approximately 70% were female.

Patients were required to have at least 1 relapse in the previous 12 months. In the overall study population, the mean duration of MS prior to study enrolment was 8.7 years, and the median baseline neurological disability based on Expanded Disability Status Scale (EDSS) score across all treatment groups was 3.0 (range 0 to 6.0). Over two thirds of the study patients were treatment-naive for MS disease-modifying drugs (DMDs). Approximately 29% of patients had received treatment with other disease modifying therapies prior to entering the study, with interferon-beta and glatiramer acetate being the most commonly used prior therapies (used by 28.7% and 6.5% of all patients, respectively).

The primary objective was to evaluate the efficacy of MAVENCLAD versus placebo in the reduction of annualized relapse rate (ARR) during 96 weeks of treatment in patients with RRMS. The secondary objectives were to assess the effect of MAVENCLAD on slowing disability progression (EDSS) and decreasing active lesions as measured by MRI.

**Study results**
Patients with relapsing-remitting MS receiving MAVENCLAD 3.5 mg/kg showed statistically significant improvements in the annualized relapse rate compared to patients on placebo (see Table 6).

**Table 6 Clinical outcomes in the CLARITY study (96 weeks)**

| Parameter | Placebo (n = 437) | MAVENCLAD cumulative dose 3.5 mg/kg (n = 433) |
|---|---|---|
| Annualized relapse rate (95% CI) | 0.33 (0.29, 0.38) | 0.14* (0.12, 0.17) |
| Relative reduction (cladribine vs. placebo) | | 57.6% |

* $p < 0.001$ compared to placebo

For secondary MRI endpoints, the MAVENCLAD 3.5 mg/kg treatment group was statistically significantly superior to placebo with regard to number and relative reduction of T1 Gd+ lesions, active T2 lesions and Combined Unique Active (CUA) lesions as demonstrated in brain MRI over the entire 96 weeks of the study. Patients taking MAVENCLAD compared to the placebo treatment group had 86% relative reduction in the mean number of T1 Gd+ lesions, 73% relative reduction in the mean number of active T2 lesions and 74% relative reduction in the mean number of CUA lesions per patient per scan ($p < 0.001$ across all 3 MRI outcomes).

Other secondary endpoints included the proportion of patients relapse-free over 96 weeks and time to 3-month EDSS progression. The proportion of patients relapse-free over 96 weeks was greater for those receiving MAVENCLAD 3.5 mg/kg compared to those receiving placebo (79.7% vs 60.9%). Treatment with MAVENCLAD 3.5 mg/kg prolonged the time to 3-month sustained change in EDSS score compared to placebo. Tertiary endpoints included time to first relapse. Treatment with MAVENCLAD 3.5 mg/kg prolonged the time to first relapse compared to placebo.

## DETAILED PHARMACOLOGY

Pharmacokinetic interactions

By complex formation, the hydroxypropyl betadex component of the MAVENCLAD tablet may enhance the solubility of and thereby increase systemic exposure to low soluble drugs when co-administered with MAVENCLAD.

*In vitro* studies have shown that cladribine is not a substrate for CYP enzymes and does not show significant potential to act as an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. Inhibition of one of these enzymes, or genetic polymorphisms (e.g. CYP2D6, CYP2C9 or CYP2C19), is not expected to result in clinically significant effects on cladribine pharmacokinetics. Cladribine had no clinically meaningful inductive effect *in vitro* on CYP1A2, CYP2B6 and CYP3A4 enzymes.

*In vitro* studies indicate that cladribine efflux by the P-glycoprotein (P-gp) is minimal. Clinically relevant interactions with inhibitors or inducers of P-gp are not expected.

At the level of gastrointestinal or kidney efflux, *in vitro* studies have shown that cladribine is a substrate for BCRP. Inhibition of BCRP/ABCG2 may theoretically increase the oral bioavailability and systemic exposure of cladribine.

*In vitro* studies indicate that cladribine is substrate of nucleoside transport proteins ENT1, ENT2, CNT2 and CNT3. Accordingly, the bioavailability, intracellular distribution and renal elimination of cladribine may theoretically be altered by potent ENT and CNT transporter inhibitors. However, the potential alteration in cladribine exposure, and hence the clinical relevance of these findings is unknown.

Published *in vitro* data had indicated that cladribine could be degraded at acidic pH. However, drug interaction studies in vivo showed that the bioavailability of 10 mg MAVENCLAD was not altered when co-administered with pantoprazole, and the bioavailability of cladribine oral solution was not enhanced when co-administered with omeprazole.

## TOXICOLOGY

Non-clinical safety assessment of cladribine in mice and monkeys revealed findings that could mainly be attributed to the pharmacologic mechanism of the drug. These included decreases in lymphocyte and other blood cell counts, lymphoid depletion from lymphoid tissues, bone marrow depletion or fatty change, renal toxicity (renal tubular degeneration and karyomegaly), gastrointestinal toxicity (mucosal atrophy or necrosis), and testicular effects (see TOXICOLOGY, Reproductive toxicity; TOXICOLOGY, Fertility). Atrophy of the zona reticularis and decreased vacuolization in the zona fasciculata in the adrenal gland were also observed in monkeys in the 1-year study, but not reported in any other study.

While exposure margins were not high in the monkeys, particularly in the 1-year study, findings were considered reversible and generally mild, and therefore it is not anticipated that cladribine would pose significant risk to MS patients at the recommended intermittent and infrequent dose regimen proposed for the MS indication, with the exception of reproductive toxicity as described below.

Genotoxicity

Cladribine was genotoxic, causing chromosomal damage in the bone marrow of mice *in vivo* and in mammalian cells *in vitro* without and with rat liver metabolic activation. These findings are expected since cladribine can cause inhibition of DNA synthesis and repair and DNA strand breaks by mechanisms that involve incorporation into DNA, an imbalance of deoxynucleotide triphosphate pools, and/or depletion of intracellular nicotinamide adenine dinucleotide. Cladribine was not mutagenic in bacterial (Ames) and *in vitro* mammalian cell assays. *In vivo* clastogenicity in mice was detected at 10 mg/kg, which was the lowest dose tested.

Carcinogenicity

The carcinogenic potential of cladribine was assessed in a 22-month s.c. study in mice and in a short-term, 6-month, study by oral route in Tg rasH2 mice. In the 22--month study, cladribine was administered using a cyclic dosing schedule of seven days of treatment followed by a 21-day drug free period for approximately 22 cycles at doses of 0.1, 1.0, and 10 mg/kg/day. In the 6-month carcinogenicity study, cladribine tablets (drug product formulated with 2-hydroxypropyl-β-cyclodextrin) or cladribine drug substance was administered to Tg rasH2 mice using a cyclic dosing schedule of five days of treatment followed by a 23-day drug free period for 6 cycles plus five additional days of treatment at doses of 5, 15, and 30 mg/kg/day.

The only treatment-related neoplastic finding was a higher incidence of mainly benign Harderian gland tumors in male and female CD-1 mice given 10 mg/kg/day, which is not considered to represent a risk for patients, since humans do not have an equivalent anatomic structure. Systemic exposure to cladribine at the 10 mg/kg/day dose level in CD-1 mice was estimated to be about 15 times that expected in patients taking 20 mg doses, while that at 30 mg/kg/day in transgenic mice was about 25 times that in patients.

Reproductive toxicity

While there were no effects on fertility, reproductive function or general performance of offspring, cladribine was embryo-lethal when administered to pregnant mice and was teratogenic in mice and rabbits. The observed embryo-lethal and teratogenic effects are consistent with the pharmacologic mechanisms of cladribine.

In a male mouse fertility study, malformed fetuses with agenesis of portions of appendage(s) distal to the humerus and/or femur were seen. The incidence of affected mouse fetuses in this study was in the same range of spontaneous incidence of amelia and phocomelia in this strain of mice and these changes were not considered related to cladribine administration. However, considering cladribine genotoxicity, male-mediated effects related to potential genetic alteration of differentiating sperm cells cannot be excluded.

In female mice, cladribine was administered s.c. once daily beginning 14 days prior to cohabitation with untreated males, continuing through the cohabitation period, and ending on day 6 of gestation at 1, 2, 4, or 8 mg/kg/day (24 female mice/group). Based on the results of this study, cladribine did not cause direct maternal toxicity or affect the estrus course or pregnancy rates, but was embryolethal at 8 mg/kg/day. The No Observed Adverse Effect Level (NOAEL) was 4 mg/kg/day.

Cladribine was administered i.v. to pregnant mice at doses of 0.5, 1.5, or 3.0 mg/kg/day from days 6 through 15 of gestation. A significant increase in variations of fetal growth/development (i.e. increases in cervical ribs, irregularly-shaped exoccipital bones, and variations in sternal ossification) was seen at 1.5 mg/kg/day and increased resorptions, reduced litter size and increased fetal malformations were seen at 3 mg/kg/day (mainly exencephaly and skeletal variations). No fetal effects were seen at 0.5 mg/kg/day. The NOAEL was 3 mg/kg/day for the adult pregnant female and 0.5 mg/kg/day for the fetus.

Cladribine was administered i.v. to pregnant New Zealand White rabbits once daily during the period of organogenesis at 0.3, 1.0, or 3.0 mg/kg/day from days 7 through 19 of gestation. There was no evidence of maternal toxicity. Cladribine was teratogenic at 3.0 mg/kg/day, which manifested primarily as numerous limb anomalies. There was also a significant decrease in the mean fetal weight at this dosage level. The NOAEL was 3.0 mg/kg/day for maternal toxicity, and 1.0 mg/kg/day for embryo-fetal toxicity.

Mated female mice were administered cladribine i.v. at 0.5, 1.5, or 3.0 mg/kg/day from implantation to the end of lactation. There was no evidence of maternal toxicity. An increase in fetal skeletal variations was seen at 1.5 mg/kg/day. At 3.0 mg/kg/day, exencephaly and/or open eyelid in dead offspring, a decrease in the number of live offspring and birth index, and an increase of skeletal anomalies and variations were seen. No adverse effects on reproductive functions or general performance of the offspring were seen. Based on the results of this study, the NOAEL for maternal reproductive function and general toxicity was 3 mg/kg/day while the NOAEL for developmental toxicity in the offspring was 0.5 mg/kg/day.

Fertility

Cladribine at daily doses of 1, 5, 10, or 30 mg/kg/day given subcutaneously for 28 days prior to cohabiting with untreated females did not affect the fertility of male mice, but testicular effects were indicated by reduced testicular weights at 10 and 30 mg/kg/day and increased numbers of non-motile sperm at 30 mg/kg/day. The 5 mg/kg/day dose was a no-effect level at which systemic exposure to cladribine was estimated to be about 8 times that in MS patients taking 20 mg/day.

Testicular degeneration was seen in one monkey at 1.0 mg/kg/day in the one year s.c. study, where 0.3 mg/kg/day was a no-effect dose at which systemic exposure was probably similar to that in patients. Decreased sperm motility, in the absence of microscopic correlates, was observed in monkeys given an intermittent oral dose of 6 mg/kg/day for 3 cycles, with 3 mg/kg/day a no-effect dose at which systemic exposure to cladribine was variable, but generally less than that in patients taking 20 mg/day.

Reduced testes weight and degeneration of seminiferous tubules or signs of atrophy of germinal epithelium were seen in the oral 4-month study in CD-1 mice (combination study) and 26-week carcinogenicity study in Tg rasH2 mice at 30 mg/kg/day, as well as in a 3-month subcutaneous study at 10 and 30 mg/kg/day in CD-1 mice. The fertility of female mice was unaffected at s.c. doses up to 8 mg/kg/day.

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**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

**PATIENT MEDICATION INFORMATION**

**MAVENCLAD™**
**Cladribine 10 mg tablets**

Read this carefully before you start taking MAVENCLAD and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about MAVENCLAD.

**What is MAVENCLAD used for?**

- MAVENCLAD is used to treat adult patients with relapsing-remitting multiple sclerosis (RRMS). Multiple sclerosis (MS) is a disease that affects the brain and spinal cord.
- Treatment with MAVENCLAD has been shown to reduce the frequency of relapses and to slow down disability progression.
- MAVENCLAD is generally recommended for MS patients who have not responded well to, or cannot tolerate one or more of the other therapies for MS.

**How does MAVENCLAD work?**

Cladribine, the active substance in MAVENCLAD is cytotoxic, which means it causes cell death. Cladribine acts in specific ways on cells in your immune system called B and T lymphocytes. Cladribine helps to reduce inflammation in your body as a result of having MS.

**What are the ingredients in MAVENCLAD?**

Medicinal ingredients: cladribine
Non-medicinal ingredients: hydroxypropyl betadex, sorbitol and magnesium stearate.

**MAVENCLAD comes in the following dosage forms:**

10 mg tablet

**Do not use MAVENCLAD if you:**

- are allergic (hypersensitive) to cladribine or any of the other ingredients of MAVENCLAD;
- are at risk for infections because you have a weak immune system due to:
    - treatments you receive (for cancer [medication or radiation], chronic corticosteroids, bone marrow transplant(s), etc.);
    - a medical condition you have (for example, if you are infected with the human

immunodeficiency virus [HIV]);
- have an active or inactive (past) infection, for example tuberculosis or liver inflammation (hepatitis);
- have or had a type of rare infection of the brain called progressive multifocal leukoencephalopathy (PML);
- have an active cancer;
- have moderate or severe kidney problems;
- are pregnant or breast-feeding.

Talk to your healthcare professional if you are unsure if any of the above applies to you.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take MAVENCLAD. Talk about any health conditions or problems you may have, including if you:**

- have a weakened immune system due to:
    - treatments you receive (for cancer [medication or radiation], bone marrow transplant(s), etc.);
    - a medical condition you have (for example, if you are infected with the human immunodeficiency virus [HIV]);
- have an infection;
- have liver problems;
- have recently been vaccinated;
- have or have previously had cancer;
- require blood transfusions;
- are pregnant, are thinking of becoming pregnant as MAVENCLAD may harm your baby;
- are breast-feeding;
    - it is not known if MAVENCLAD goes into breast milk
    - if your healthcare professional believes that MAVENCLAD is essential for you, they should advise you to stop breast-feeding
- are less than 18 years of age.

**Other warnings you should know about:**

Blood Tests

You will have blood tests taken before you start treatment to see if you can take MAVENCLAD. Your healthcare professional will also do blood tests during and after treatment to ensure you can continue to take MAVENCLAD. The tests will determine if you are developing any complications from the treatment.

General Infections

You will be tested to see if you have any infections prior to starting MAVENCLAD. It is important to talk to your healthcare professional if you think you have an infection before, during or after treatment. Symptoms of infections can include:

- fever
- aching, painful muscles

- headache
- generally feeling unwell
- loss of appetite

Your healthcare professional may delay start of treatment, or interrupt current treatment, until the infection clears up.

Vaccination
Talk to your healthcare professional if you have recently been given, or might be given, certain vaccines (called 'live' or 'live attenuated' vaccines).

- Treatment with MAVENCLAD can only begin 6 weeks after you have been vaccinated.
- If necessary, you will be vaccinated against varicella (chickenpox) prior to starting treatment.
- You must not be vaccinated during treatment with MAVENCLAD.
- You may only be vaccinated after MAVENCLAD treatment when your white blood cell count is normal.

Progressive Multifocal Leukoencephalopathy (PML)
Talk to your healthcare professional if you believe your MS is getting worse or if you notice any new symptoms, such as:

- weakness on one side of the body that gets worse
- clumsiness of your arms and legs
- trouble with your vision
- changes in your thinking and memory that lead to confusion and personality changes

These may be the symptoms of a rare brain disorder caused by infection and called progressive multifocal leukoencephalopathy (PML). PML is a serious condition that may lead to severe disability or death.

As a precaution, you may have a head MRI (magnetic resonance imaging) prior to starting treatment. This is particularly important if you have previously taken other multiple sclerosis treatments where PML is a risk.

Risk of Cancer
MAVENCLAD causes damage to the DNA (genotoxicity) and suppresses the immune system. As a result, MAVENCLAD could potentially increase the risk of cancer. In studies with MAVENCLAD, there were single cases of patients who developed different types of cancer, such as skin, ovarian, thyroid, breast and pancreatic cancer.

Follow your healthcare professional's instructions for screening for cancer.

Fructose Intolerance
MAVENCLAD contains sorbitol. Do not take MAVENCLAD if you have hereditary problems of fructose intolerance.

Pregnancy and Fertility

- It is important that:
  - women taking MAVENCLAD prevent pregnancy during treatment and for at least 6 months after the last dose.
  - men taking MAVENCLAD prevent pregnancy in their female partner while they are taking MAVENCLAD and for at least 6 months after the last dose.
- For female patients, it is not known if MAVENCLAD will reduce the efficacy of birth control pills. Given this, a barrier method of contraception (for example, condoms) should be added during treatment with MAVENCLAD and for at least 4 weeks after the last dose in each treatment year.
- If you or your partner gets pregnant during treatment or within the 6 months after the last dose, there may be a risk to the unborn baby. Your healthcare professional will stop treatment with MAVENCLAD if you are a woman and you get pregnant while taking it.
- MAVENCLAD may affect male fertility. Talk to your healthcare professional for more information.

**Tell your healthcare professional if you are taking, have recently taken or might take any other medicines including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

Do not take MAVENCLAD together with medicines that weaken your immune system or your bone marrow. These include:

- cyclosporine, cyclophosphamide or azathioprine, used to suppress the immune system, for example after organ transplantation;
- methotrexate, used to treat conditions such as psoriasis or rheumatoid arthritis;
- long-term corticosteroids, used to reduce inflammation, for example in asthma. (Short-term corticosteroids can be used when advised by your healthcare professional).

Do not take MAVENCLAD at the same time as any other medicine. It may interact with other medicines in your stomach. Take other medicines 3 hours before or after you take MAVENCLAD.

Talk to your healthcare professional, if you are or have been treated with:

- medicines which may affect your blood cells (for example, carbamazepine used to treat convulsions). Your healthcare professional may need to supervise you more closely.
- dipyridamole, dilazep, nifedipine, nimodipine, reserpine, cilostazol or sulindac, used to treat the heart, high blood pressure, vascular conditions or inflammation
- cyclosporine (used to prevent organ transplant rejection)
- gefitinib, imatinib (used to treat cancer)
- elvitegravir, cobicistat (used to treat HIV/AIDS)
- eltrombopag (used to treat blood disorders)
- long-term corticosteroids (used to suppress inflammation)

**How to take MAVENCLAD:**

*A. Understanding the MAVENCLAD Packaging*

Follow the steps below for opening the MAVENCLAD package and for how to handle the tablets. As MAVENCLAD is cytotoxic, it is important that you follow the instructions below to make sure you handle and take MAVENCLAD safely.

1. Have a glass of water ready and make sure your hands are clean and dry before taking the tablet(s).
2. Pick up the carton with the instructions facing up.
3. Open the package as follows (see Figure A below):
   i. Open the flap on the left end.
   ii. Push in both hooks on the sides of the carton. Use your index finger and thumb and keep the hooks pushed in.
   iii. Pull the tray out until it stops. Do not try to remove the tray from the carton. It is important the tray stays in the carton to help prevent anyone from touching the tablets, especially children.

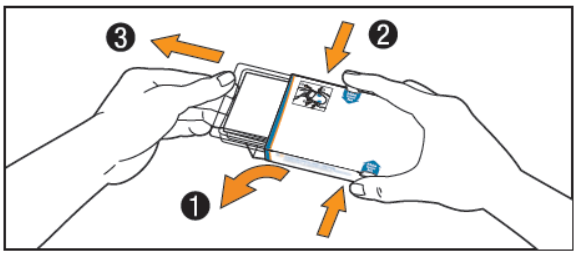


**FIGURE A**

4. Take the Package Insert out from the tray and read through all of it before taking MAVENCLAD.
5. Raise the blister pack by pushing your finger through the hole in the tray (see Figure B below). Place your hand under the blister pack and push 1 or 2 tablet(s) into your hand, based on your prescribed dose.

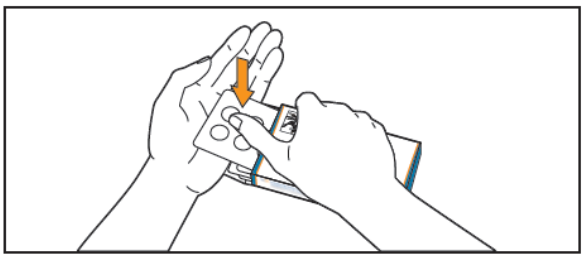

**FIGURE B**

6. Tablets must be swallowed whole and not chewed or allowed to dissolve in your mouth. Swallow the tablet(s) with water immediately after removing them from the blister.
   i. Do not leave your tablet(s) exposed on surfaces, for example on a table, or handle the tablet longer than necessary.
   ii. If a tablet is left on a surface or if a broken or fragmented tablet is released from the blister, the area must be thoroughly washed.

iii. If you lose a tablet, contact your healthcare professional for advice.

7. **Wash your hands thoroughly with soap and water before touching your nose, eyes, and other parts of the body**.
8. Push the tray back into the carton.
9. Keep your tablets in the blister until your next dose. It is important that the tablets stay in the blister to help prevent anyone from touching the tablets or taking it by mistake.

*B. Understanding Your Treatment Courses*

You will be given MAVENCLAD as **two treatment courses** over **2 years**.

One treatment course is **2 treatment weeks**, which are taken one month apart at the beginning of each treatment year.

A **treatment week** consists of **1 or 2 tablets daily given for 4 or 5 days**.

*Example:* if you start your treatment mid-April, you take your tablets as shown.

| **Year 1** | | **Year 2** | |
|---|---|---|---|
| 1st treatment week | 1 or 2 tablets daily for 4 or 5 days, mid-April | 1st treatment week | 1 or 2 tablets daily for 4 or 5 days, mid-April |
| 2nd treatment week | 1 or 2 tablets daily for 4 or 5 days, mid-May | 2nd treatment week | 1 or 2 tablets daily for 4 or 5 days, mid-May |

Before you start a treatment course, your healthcare professional will do a blood test to see whether the levels of lymphocytes (a type of white blood cells) are in an acceptable range. If this is not the case, your treatment will be delayed.

Once you have completed the 2 treatment years, your healthcare professional will observe your condition for another 2 years, in which you do not need to take the medicine. The efficacy of taking MAVENCLAD for longer than 2 years has not yet been established.

**Usual dose:**

Always take MAVENCLAD exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure. Take the tablet(s) at about the same time each day. You do not have to take the tablets at meal times. You can take them with or without food. Your healthcare professional may recommend that you take any other oral medication 3 hours before or after you take MAVENCLAD.

1. You will be prescribed the correct number of tablets for each treatment week, based on your body weight according to the table below.
2. In the left column of the table below find the row that fits your body weight (in kg), and then check the number of tablets that should be in the pack(s) for the treatment week you will be starting.
3. If the number of tablets in your pack(s) is different from the number shown for your weight in the table below, speak to your healthcare professional.
4. Note that for some weight ranges the number of tablets may vary from one treatment week to the next.

*Example:* if you weigh 85 kg and are about to start treatment week 1, you will be given 8 tablets.

| **Your weight in kg** | **Number of tablets to take** | | | |
|---|---|---|---|---|
| | **Year 1 treatment course** | | **Year 2 treatment course** | |
| | **Treatment week 1** | **Treatment week 2** | **Treatment week 1** | **Treatment week 2** |
| Less than 40 kg | Your healthcare professional will tell you the number of tablets to take | | | |
| 40 to < 50 | 4 | 4 | 4 | 4 |
| 50 to < 60 | 5 | 5 | 5 | 5 |
| 60 to < 70 | 6 | 6 | 6 | 6 |
| 70 to < 80 | 7 | 7 | 7 | 7 |
| 80 to < 90 | 8 | 7 | 8 | 7 |
| 90 to < 100 | 9 | 8 | 9 | 8 |
| 100 to < 110 | 10 | 9 | 10 | 9 |
| 110 and above | 10 | 10 | 10 | 10 |

Duration of a treatment week
Depending on the total number of tablets you have been prescribed, you have to take them over 4 or 5 days, in each treatment week.

The table below shows how many tablets (1 or 2 tablets) you have to take on each day. If your daily dose is 2 tablets, take them at the same time.

*Example:* if you have to take 8 tablets, you would take **2 tablets** on Day 1, Day 2, Day 3, then **1 tablet** on Day 4 and Day 5.

| **Total number of tablets per treatment 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 you have any further questions on the use of this medicine, ask your healthcare professional.

**Overdose:**

If you think you have taken too much MAVENCLAD™, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

There is limited experience with overdose of MAVENCLAD. It is known that the more medicine you take the less lymphocytes may be present in your body, resulting in lymphopenia.

**Missed Dose:**

| **If you miss a dose and you remember on the same day you were supposed to take it** | **If you miss a dose and do not remember it until the following day** |
|---|---|
| Take the missed dose on that day. | Do not take the missed dose along with the next scheduled dose.<br>Take the missed dose on the next day and extend the number of days in that treatment week. |

Example: If you forget to take the Day 3 dose and do not remember it until Day 4, take the Day 3 dose on Day 4, and extend the total number of days in the treatment week by 1 day. If you miss 2 consecutive doses (for example both Day 3 and Day 4 doses), take the missed doses for the next 2 days, and then extend the treatment week by 2 days.

If you have any further questions on the use of this medicine, ask your healthcare professional.

**What are possible side effects from using MAVENCLAD?**

These are not all the possible side effects you may feel when taking MAVENCLAD. If you experience any side effects not listed here, contact your healthcare professional.

**Very common side effects:** may affect more than 1 in 10 people
- Nausea
- Headache

**Common side effects:** may affect up to 1 in 10 people
- Cold sores (oral herpes)
- Rash
- Thinning or hair loss
- Fever
- Abdominal pain
- Toothache
- Flu and flu like symptoms
- Cold symptoms
- Bronchitis or other chest infections
- Symptoms of gastroenteritis (diarrhea, vomiting, abdominal pain)
- Back pain
- Anxiety
- Vaginal infection

| Serious side effects and what to do about them | | | |
|---|---|---|---|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| **VERY COMMON**<br>Reduction in the number of certain white blood cells, with symptoms such as infections, feeling unusually tired, fever, aches, pain and flu-like symptoms. | | ✓ | |
| **COMMON**<br>Shingles, with symptoms such as localized 'band' of severe pain and blistering rash, typically on one side of the upper body or the face. Other symptoms may be headache, burning, tingling, numbness or itchiness of the skin in the affected area, feeling generally unwell or fever in the early stages of infection. | | ✓ | |
| **VERY RARE**<br>Tuberculosis, with symptoms such as cough that does not go away, fever or loss of weight. | | ✓ | |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

**Reporting Side Effects**
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
**3 ways to report**:

- Online at MedEffect (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

*NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:**

- Store MAVENCLAD at room temperature (15°C to 30°C).
- Store this medicine in the original package in order to protect from moisture.
- Keep out of reach and sight of children.

**If you want more information about MAVENCLAD:**

- Talk to your healthcare professional.
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); or by calling the manufacturer: 1-888-677-3243.

This leaflet was prepared by EMD Serono, a Division of EMD Inc., Canada.

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