MAVENCLAD®
Cladribine

1. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 10 mg of cladribine.

Excipients with known effect: Each tablet contains 64 mg sorbitol.

For the full list of excipients, see section 5.1 List of Excipients.

2. PHARMACEUTICAL FORM
Tablet.

White, round, biconvex tablets of 8.5 mm diameter, engraved with 'C' on one side and '10' on the other side.

3. CLINICAL PARTICULARS
3.1 Indications
MAVENCLAD is indicated for the treatment of adult patients with relapsing-remitting multiple sclerosis (MS) as defined by clinical or imaging features (*see section 4.1 Pharmacodynamic Properties*).

3.2 Posology and Method of Administration
Treatment with MAVENCLAD must be initiated and supervised by a physician experienced in the treatment of MS.

Posology
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. 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 treatment year. If medically necessary (e.g. for recovery of lymphocytes), the treatment course in year 2 can be delayed for up to 6 months. 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. For details, see Tables 1 and 2 below.

Following completion of the 2 treatment courses, no further cladribine treatment is required in years 3 and 4 (*see section 4.1 Pharmacodynamic Properties*). Re-initiation of therapy after year 4 has not been studied.

Criteria for initiating and continuing therapy
Lymphocyte counts must be
- normal before initiating MAVENCLAD in year 1,
- at least 800 cells/mm³ before initiating MAVENCLAD in year 2.

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.

Distribution of dose

The distribution of the total dose over the 2 years of treatment is provided in Table 1. 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 1 Dose of MAVENCLAD per treatment week by patient weight in each treatment year

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

Table 2 shows how the total number of tablets per treatment week is distributed over the individual days. It is recommended that the daily cladribine 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 2 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

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. If two consecutive doses are missed, the same rule applies, and the number of days in the treatment week is extended by two days.

Concomitant use of other oral medicinal products

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 (*see section 3.5 3.5 Interaction with Other Medicinal Products and Other Forms of Interaction*).

Special populations

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 (*see section 4.2 Pharmacokinetic Properties*).

Safety and efficacy in patients with moderate or severe renal impairment have not been established. Therefore, MAVENCLAD is contraindicated in these patients (*see section 3.3 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 section 4.2 Pharmacokinetic Properties*), in the absence of data, use of MAVENCLAD is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh score >6).

Elderly
Clinical studies with oral cladribine in MS did not include patients over 65 years of age; therefore, it is not known 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.

Paediatric population
The safety and efficacy of MAVENCLAD in patients below the age of 18 years have not been established. No data are available.

Method of administration
MAVENCLAD is for oral use. The tablets must be taken with water, and swallowed without chewing. The tablets can be taken independent of food intake.

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.

3.3 Contraindications
- Hypersensitivity to the active substance or to any of the excipients listed in section 5.1 List of Excipients.
- Infection with human immunodeficiency virus (HIV).
- Active chronic infection (tuberculosis or hepatitis).
- Initiation of cladribine treatment in immunocompromised patients, including patients currently receiving immunosuppressive or myelosuppressive therapy (*see section 3.5 Interaction with Other Medicinal Products and Other Forms of Interaction*).
- Active malignancy.
- Moderate or severe renal impairment (creatinine clearance <60 mL/min) (*see section 4.2 Pharmacokinetic Properties*).
- Pregnancy and breast-feeding (*see section 3.6 Pregnancy and Lactation*).

3.4 Special Warnings and Special Precautions for Use

Haematological monitoring

Cladribine's mode of action is closely linked to a reduction in lymphocyte count. The effect on lymphocyte count is dose-dependent. Decreases in neutrophil count, red blood cell count, haematocrit, haemoglobin or platelet count compared to baseline values have also been observed in clinical studies, although these parameters usually remain within normal limits.

Additive haematological adverse reactions may be expected if cladribine is administered prior to or concomitantly with other substances that affect the haematological profile (*see section 3.5 Interaction with Other Medicinal Products and Other Forms of Interaction*).

Lymphocyte counts must be determined

- 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/mm³, it should be actively monitored until values increase again.

For treatment decisions based on the patient's lymphocyte counts, see section 3.2 Posology and Method of Administration and subsection 'Infections' below.

Infections

Cladribine can reduce the body's immune defence and may increase the likelihood of infections. HIV infection, active tuberculosis and active hepatitis must be excluded before initiation of cladribine (*see section 3.3 Contraindications*).

Latent infections may be activated, including tuberculosis or hepatitis. Therefore, screening for latent infections, in particular tuberculosis and hepatitis B and C, must be performed prior to initiation of therapy in year 1 and year 2. Initiation of MAVENCLAD should be delayed until the infection has been adequately treated.

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

Particular attention is recommended for patients who have no history of exposure to varicella zoster virus. Vaccination of antibody-negative patients is recommended prior to initiation of cladribine therapy. Initiation of treatment with MAVENCLAD should be postponed for 4 to 6 weeks to allow for the full effect of vaccination to occur.

The incidence of herpes zoster was increased in patients on cladribine. If lymphocyte counts drop below 200 cells/mm³, anti-herpes prophylaxis according to local standard practice should be considered during the time of grade 4 lymphopenia (*see section 3.8 Undesirable Effects*).

Patients with lymphocyte counts below 500 cells/mm³ should be actively monitored for signs and symptoms suggestive of infections, in particular herpes zoster. If such signs and symptoms occur, anti-infective treatment should be initiated as clinically indicated. Interruption or delay of MAVENCLAD may be considered until proper resolution of the infection.

Cases of progressive multifocal leukoencephalopathy (PML) have been reported for parenteral cladribine in patients treated for hairy cell leukaemia with a different treatment regimen.

In the clinical study data base of cladribine in MS (1,976 patients, 8,650 patient years) no case of PML has been reported. However, a baseline magnetic resonance imaging (MRI) should be performed before initiating MAVENCLAD (usually within 3 months).

Malignancies
In clinical studies, events of malignancies were observed more frequently in cladribine-treated patients compared to patients who received placebo (*see section 3.8 Undesirable Effects*).

MAVENCLAD is contraindicated in MS patients with active malignancies (*see section 3.3 Contraindications*). 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.

Liver function
Liver injury, including serious cases, has been reported uncommonly 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. Patients should have their serum aminotransferase, alkaline phosphatase, and total bilirubin levels assessed prior to initiation of therapy in year 1 and year 2. During treatment, liver enzyme and bilirubin monitoring should be obtained based on clinical signs and symptoms.

If a patient develops clinical signs, unexplained liver enzyme elevations or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine), serum transaminases and total bilirubin should be measured promptly. Treatment with MAVENCLAD should be interrupted or discontinued, as appropriate.

Contraception
Before initiation of treatment both in year 1 and year 2, women of childbearing potential and males who could potentially father a child should be counselled regarding the potential for serious risk to the foetus and the need for effective contraception (*see section 3.6 Pregnancy and Lactation*).

Women of childbearing potential must prevent pregnancy by use of effective contraception during cladribine treatment and for at least 6 months after the last dose (*see section 3.5 Interaction with Other Medicinal Products and Other Forms of Interaction*).

Male patients must take precautions to prevent pregnancy of their female partner during cladribine treatment and for at least 6 months after the last dose.

Blood transfusions
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 haematologist is advised.

Switching to and from cladribine treatment
In patients who have previously been treated with immunomodulatory or immunosuppressive medicinal products the mode of action and duration of effect of the other medicinal product should be considered prior to initiation of MAVENCLAD. A potential additive effect on the immune system should also be considered

when such medicinal products are used after treatment with MAVENCLAD (*see section 3.5 Interaction with Other Medicinal Products and Other Forms of Interaction*).

When switching from another MS medicinal product, a baseline MRI should be performed (see subsection 'Infections' above).

Hepatic impairment
Although the importance of hepatic function for the elimination of cladribine is considered negligible (see section 5.2), in the absence of data, use of MAVENCLAD is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh score >6) (*see section 3.2 Posology and Method of Administration*).

Sorbitol
The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

3.5 Interaction with Other Medicinal Products and Other Forms of Interaction
MAVENCLAD contains hydroxypropylbetadex, which may be available for complex formation with other medicinal products, potentially leading to an increase in bioavailability of such a product (especially medicinal products with low solubility). Therefore, 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.

Immunosuppressive medicinal products
Initiation of cladribine treatment is contraindicated in immunocompromised patients, including patients currently receiving immunosuppressive or myelosuppressive therapy with, e.g., methotrexate, cyclophosphamide, cyclosporine or azathioprine, or chronic use of corticosteroids because of a risk of additive effects on the immune system (*see section 3.3 Contraindications*).

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

Other disease-modifying medicinal products
The use of MAVENCLAD with interferon beta results in an increased risk of lymphopenia. Safety and efficacy of MAVENCLAD in combination with other disease-modifying treatments for MS have not been established. Concomitant treatment is not recommended.

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

Live or live attenuated vaccines
Treatment with MAVENCLAD should not be initiated within 4 to 6 weeks after vaccination with live or attenuated live vaccines because of a risk of active vaccine infection. Vaccination with live or attenuated live vaccines should be avoided during and after cladribine treatment as long as the patient's white blood cell counts are not within normal limits.

Potent ENT1, CNT3 and BCRP transporter inhibitors
At the level of cladribine absorption, the only conceivable interaction pathway of clinical relevance appears to be the breast cancer resistance protein (BCRP or ABCG2). Inhibition of BCRP in the gastrointestinal tract may increase the oral bioavailability and systemic exposure of cladribine. Known BCRP inhibitors, which may alter the pharmacokinetics of BCRP substrates by 20% *in vivo*, include eltrombopag.

In vitro studies indicate that cladribine is a substrate of the equilibrative nucleoside (ENT1) and concentrative nucleoside (CNT3) transport proteins. Accordingly, the bioavailability, intracellular distribution and renal elimination of cladribine may theoretically be altered by potent ENT1 and CNT3 transporter inhibitors such as dilazep, nifedipine, nimodipine, cilostazol, sulindac or reserpine. However, net effects in terms of potential cladribine exposure alterations are difficult to predict.

Although the clinical relevance of such interactions is unknown, it is recommended that co-administration of potent ENT1, CNT3 or BCRP inhibitors be avoided during the 4- to 5-day cladribine treatment. If this is not possible, selection of alternative concomitant medicinal products with no, or minimal ENT1, CNT3 or BCRP 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 and P-gp transporter inducers
The effects of potent inducers of the efflux transporters BCRP and P-glycoprotein (P-gp) on the bioavailability and disposition of cladribine have not been formally studied. A possible decrease in cladribine exposure should be considered if potent BCRP (e.g. corticosteroids) or P-gp (e.g. rifampicin, St. John's Wort) transporter inducers are co-administered.

Hormonal contraceptives
It is currently unknown whether cladribine may reduce the effectiveness of systemically acting hormonal contraceptives. Therefore, women using systemically acting hormonal contraceptives should add a barrier method during cladribine treatment and for at least 4 weeks after the last dose in each treatment year (*see section 3.6 Pregnancy and Lactation*).

3.6 Pregnancy and Lactation
Contraception in males and females
Before initiation of treatment both in year 1 and year 2, women of childbearing potential and males who could potentially father a child should be counselled regarding the potential for serious risk to the foetus and the need for effective contraception.

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 cladribine treatment and for at least 6 months after the last dose. Women using systemically acting hormonal contraceptives should add a barrier method during cladribine treatment and for at least 4 weeks after the last dose in each treatment year (*see section 3.5 Interaction with Other Medicinal Products and Other Forms of Interaction*). Women who become pregnant under therapy with MAVENCLAD should discontinue treatment.

As cladribine interferes with DNA synthesis, adverse effects on human gametogenesis could be expected (*see section 4.3 Preclinical Safety Data*). Therefore, male patients must take precautions to prevent pregnancy of their partner during cladribine treatment and for at least 6 months after the last dose.

Pregnancy
Based on human experience with other substances inhibiting DNA synthesis, cladribine could cause congenital malformations when administered during pregnancy. Studies in animals have shown reproductive toxicity (*see section 4.3 Preclinical Safety Data*).

MAVENCLAD is contraindicated in pregnant women (*see section 3.3 Contraindications*).

Breast-feeding
It is not known whether cladribine is excreted in human milk. Because of the potential for serious adverse reactions in breast-fed infants, breast-feeding is contraindicated during treatment with MAVENCLAD and for 1 week after the last dose (*see section 3.3 Contraindications*).

Fertility
In mice, there were no effects on fertility or the reproductive function of offspring. However, testicular effects were observed in mice and monkeys (*see section 4.3 Preclinical Safety Data*).

As cladribine interferes with DNA synthesis, adverse effects on human gametogenesis could be expected. Therefore, male patients must take precautions to prevent pregnancy of their partner during cladribine treatment and for at least 6 months after the last dose (see above).

3.7 Effects on Ability to Drive and Use Machines
MAVENCLAD has no or negligible influence on the ability to drive and use machines.

3.8 Undesirable Effects
Summary of the safety profile
The most clinically relevant adverse reactions reported in MS patients who received cladribine 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 or 4 lymphopenia (<500 to 200 cells/mm^3 or <200 cells/mm^3) compared to the time when the patients were not experiencing grade 3 or 4 lymphopenia (*see section 3.4 Special Warnings and Special Precautions for Use*).

List of adverse reactions
Adverse reactions described in the list below are derived from pooled data from clinical studies in MS in which oral cladribine was used as monotherapy at a cumulative dose of 3.5 mg/kg. The safety database from these studies comprises 923 patients. Adverse reactions identified during post-marketing surveillance are indicated by an asterisk [*].

The following definitions apply to the frequency terminology used hereafter:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Frequency not known (cannot be estimated from the available data)

<u>Infections and infestations</u>
Common: Oral herpes, dermatomal herpes zoster.
Very rare: Tuberculosis (*see section 3.4 Special Warnings and Special Precautions for Use*).

Blood and lymphatic system disorders
Very common: Lymphopenia.
Common: Decrease in neutrophil count.

Immune system disorders
Common: Hypersensitivity* including pruritus, urticaria, rash and rare cases of angio-oedema.

Hepatobiliary disorders
Uncommon: Liver Injury.

Skin and subcutaneous tissue disorders
Common: Rash, alopecia.

Description of selected adverse reactions

Lymphopenia

In clinical studies, 20% to 25% of the patients treated with a cumulative dose of cladribine 3.5 mg/kg over 2 years as monotherapy developed transient grade 3 or 4 lymphopenia. Grade 4 lymphopenia was seen in less than 1% of the patients. 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). 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 (*see section 3.4 Special Warnings and Special Precautions for Use*) and strict criteria for initiating and continuing cladribine treatment must be followed (*see section 3.2 Posology and Method of Administration*).

Malignancies

In clinical studies and long-term follow-up of patients treated with a cumulative dose of 3.5 mg/kg oral cladribine, events of malignancies were observed more frequently in cladribine-treated patients (10 events in 3,414 patient-years [0.29 events per 100 patient-years]) compared to patients who received placebo (3 events in 2,022 patient-years [0.15 events per 100 patient-years]) (*see section 3.4 Special Warnings and Special Precautions for Use*).

Hypersensitivity

In clinical studies of patients treated with a cumulative dose of 3.5 mg/kg oral cladribine, hypersensitivity events were observed more frequently in cladribine-treated patients (11.8%) compared to patients who received placebo (8.4%). Serious hypersensitivity events were observed in 0.3% of cladribine-treated patients and in no patients who received placebo. Hypersensitivity events led to treatment discontinuation in 0.4% of cladribine-treated patients and in 0.3% patients who received placebo.

Liver Injury

During post-marketing experience, uncommon events of liver injury, including serious cases and cases leading to discontinuation of treatment, were reported in temporal association with MAVENCLAD.

Transient elevations of serum transaminases were usually greater than 5-fold the upper limit of normal (ULN). Isolated cases of transient serum transaminase elevations up to 40-fold the ULN and / or symptomatic hepatitis with transient elevation of bilirubin and jaundice have been observed.

Time to onset varied, with most cases occurring within 8 weeks after the first treatment course (*see section 3.4 Special Warnings and Special Precautions for Use*).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to PT Merck Tbk via email ICSR_SEA@merckgroup.com and/or to Pusat Farmakovigilans/MESO Nasional BPOM via subsite https://e-meso.pom.go.id/ADR.

3.9 Overdose
There is limited experience with overdose of oral cladribine. Lymphopenia is known to be dose-dependent (*see section 3.4 Special Warnings and Special Precautions for Use* and *3.8 Undesirable Effects*).

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

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

4. PHARMACOLOGICAL PROPERTIES
4.1 Pharmacodynamic Properties
Pharmacotherapeutic group: Selective Immunosuppressants, ATC code: L04AA40

Mechanism of action
Cladribine is a nucleoside analogue of deoxyadenosine. A chlorine substitution in the purine ring protects cladribine from degradation by adenosine deaminase, increasing the intracellular residence time of the cladribine prodrug. Subsequent phosphorylation of cladribine to its active triphosphate form, 2-chlorodeoxyadenosine triphosphate (Cd-ATP), is particularly efficiently achieved in lymphocytes, due to their constitutively high deoxycytidine kinase (DCK) and relatively low 5'-nucleotidase (5'-NTase) levels. A high DCK to 5'-NTase ratio favours the accumulation of Cd-ATP, making lymphocytes particularly susceptible to cell death. As a result of a lower DCK/5'-NTase ratio other bone marrow derived cells are less affected than lymphocytes. DCK is the rate limiting enzyme for conversion of the cladribine prodrug into its active triphosphate form, leading to selective depletion of dividing and non-dividing T and B cells.

The primary apoptosis-inducing mechanism of action of Cd-ATP has direct and indirect actions on DNA synthesis and mitochondrial function. In dividing cells, Cd-ATP interferes with DNA synthesis via inhibition of ribonucleotide reductase and competes with deoxyadenosine triphosphate for incorporation into DNA by DNA polymerases. In resting cells cladribine causes DNA single-strand breaks, rapid nicotinamide adenine dinucleotide consumption, ATP depletion and cell death. There is evidence that cladribine can also cause direct caspase-dependent and independent apoptosis via the release of cytochrome c and apoptosis-inducing factor into the cytosol of non-dividing cells.

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 B and T lymphocytes is thought to interrupt the cascade of immune events central to MS.

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.

Pharmacodynamic effects
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/mm^3 or <200 cells/mm^3) was seen 2 months after the first cladribine dose in each year, indicating a time gap between cladribine plasma concentrations and the maximum haematological 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 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.

Clinical efficacy and safety
Relapsing-remitting MS
Efficacy and safety of oral cladribine were evaluated in a randomised, double-blind, placebo-controlled clinical study (CLARITY) in 1,326 patients with relapsing-remitting MS. Study objectives were to evaluate the efficacy of cladribine versus placebo in reducing the annualised relapse rate (ARR) (primary endpoint), slowing disability progression and decreasing active lesions as measured by MRI.

Patients received either placebo (n = 437), or a cumulative dose of cladribine of 3.5 mg/kg (n = 433) or 5.25 mg/kg body weight (n = 456) 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. 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.

Patients were required to have at least 1 relapse in the previous 12 months. In the overall study population, the median age was 39 years (range 18 to 65), and the female to male ratio was approximately 2:1. The mean duration of MS prior to study enrolment was 8.7 years, and the median baseline neurological disability based on Kurtzke 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). The remaining patients were pre-treated with either interferon beta 1a, interferon beta 1b, glatiramer acetate or natalizumab.

Patients with relapsing-remitting MS receiving cladribine 3.5 mg/kg showed statistically significantly improvements in the annualised relapse rate, proportion of patients relapse-free over 96 weeks, proportion of patients free of sustained disability over 96 weeks and time to 3 month EDSS progression compared to patients on placebo (see Table 3).

Table 3 Clinical outcomes in the CLARITY study (96 weeks)

Parameter	Placebo (n = 437)	Cladribine cumulative dose	
		3.5 mg/kg (n = 433)	5.25 mg/kg (n = 456)
Annualised relapse rate (95% CI)	0.33 (0.29, 0.38)	0.14* (0.12, 0.17)	0.15* (0.12, 0.17)
Relative reduction (cladribine vs. placebo)		57.6%	54.5%
Proportion of patients relapse-free over 96 weeks	60.9%	79.7%	78.9%
Time to 3-month EDSS progression, 10th percentile (months)	10.8	13.6	13.6
Hazard ratio (95% CI)		0.67 (0.48, 0.93) p = 0.018	0.69 (0.49, 0.96) p = 0.026

*p <0.001 compared to placebo

In addition, the cladribine 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 lesions as demonstrated in brain MRI over the entire 96 weeks of the study. Patients taking cladribine compared to the placebo treatment group had 86% relative reduction in the mean number of T1 Gd+ lesions (adjusted mean number for cladribine 3.5 mg/kg, and placebo groups were 0.12 and 0.91, respectively), 73% relative reduction in the mean number of active T2 lesions (adjusted mean number for cladribine 3.5 mg/kg, and placebo groups were 0.38 and 1.43, respectively) and 74% relative reduction in the mean number of combined unique lesions per patient per scan (adjusted mean number for cladribine 3.5 mg/kg, and placebo groups were 0.43 and 1.72, respectively) (p <0.001 across all 3 MRI outcomes).

Post-hoc analysis of time to 6-month confirmed EDSS progression resulted in a 47% reduction of the risk of disability progression in the cladribine 3.5 mg/kg compared to placebo (hazard ratio = 0.53, 95% CI [0.36, 0.79], p <0.05); in the placebo group the 10th percentile was reached at 245 days, and not reached at all during the study period in the cladribine 3.5 mg/kg group.

As shown in Table 3 above, higher cumulative doses did not add any clinically meaningful benefit, but were associated with a higher incidence in ≥grade 3 lymphopenia (44.9% in the 5.25 mg/kg group vs. 25.6% in the 3.5 mg/kg group).

Patients who had completed the CLARITY study could be enrolled in CLARITY Extension. 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 the 96-week study period. The primary objective of this study was safety, while efficacy endpoints were exploratory.

The magnitude of the effect in reducing the frequency of relapses and slowing disability progression in patients receiving the 3.5 mg/kg dose over 2 years was maintained in years 3 and 4 (*see section 3.2 Posology and Method of Administration*).

4.2 Pharmacokinetic Properties

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

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 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.

The distribution of cladribine across biological membranes is facilitated by various transport proteins, including ENT1, CNT3 and BCRP.

In vitro studies indicate that cladribine efflux is only minimally P-gp related. Clinically relevant interactions with inhibitors of P-gp are not expected. The potential consequences of P-gp induction on the bioavailability of cladribine have not been formally studied.

In vitro studies showed negligible transporter-mediated uptake of cladribine into human hepatocytes.

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. *In vitro*, intra- versus extracellular accumulation ratios were found to be around 30 to 40 already 1 hour after cladribine exposure.

Biotransformation
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 metabolite 2-chloroadenine was 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).

Cladribine is not a relevant substrate to cytochrome P450 enzymes and does not show significant potential to act as inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. Inhibition of these enzymes or genetic polymorphisms (e.g. CYP2D6, CYP2C9 or CYP2C19) are not expected to result in clinically significant effects on cladribine pharmacokinetics or exposure. Cladribine has no clinically meaningful inductive effect on CYP1A2, CYP2B6 and CYP3A4 enzymes.

After entering the target cells, cladribine is phosphorylated to cladribine monophosphate (Cd-AMP) by DCK

(and also by deoxyguanosine kinase in the mitochondria). 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. In a study of the intracellular pharmacokinetics of Cd-AMP and Cd-ATP in patients with chronic myelogenous leukaemia, the levels of Cd-ATP were approximately half of the Cd-AMP levels.

Intracellular half-life of Cd-AMP was 15 h. Intracellular half-life of Cd-ATP was 10 h.

Elimination
Based on pooled population pharmacokinetic data from various studies, the median values for elimination 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 non-renal part of the elimination of cladribine (approximately 50%) consists of negligible hepatic metabolism and of extensive intracellular distribution and trapping of the active cladribine principle (Cd-ATP) within the targeted intracellular compartment (i.e. the lymphocytes) and subsequent elimination of intracellular Cd-ATP according to the life-cycle and elimination pathways of these cells.

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
No studies have been conducted to evaluate the pharmacokinetics of cladribine in elderly or in paediatric MS patients, or in subjects with renal or hepatic impairment.

A population kinetic analysis did not show any effect of age (range 18 to 65 years) or gender on cladribine pharmacokinetics.

<u>Renal impairment</u>
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} = 60 mL/min) is expected to decrease moderately, leading to an increase in exposure of 25%.

<u>Hepatic impairment</u>
The role of hepatic function for the elimination of cladribine is considered negligible.

Pharmacokinetic interactions
A drug interaction study in MS patients showed that the bioavailability of 10 mg oral cladribine was not

altered when co-administered with pantoprazole.

4.3 Preclinical Safety Data

Non-clinical safety pharmacological and toxicological assessment of cladribine in animal models relevant for the safety assessment of cladribine did not yield significant findings other than those predicted by the pharmacologic mechanism of cladribine. The primary target organs identified in the repeat-dose toxicology studies by parenteral routes (intravenous or subcutaneous) up to 1-year duration in mice and monkeys were the lymphoid and haematopoietic system. Other target organs after longer administration (14 cycles) of cladribine to monkeys by subcutaneous route were the kidneys (karyomegaly of renal tubular epithelium), adrenals (cortex atrophy and decreased vacuolation), gastrointestinal tract (mucosa atrophy) and testes. Effects on the kidneys were also seen in mice.

Mutagenicity

Cladribine is incorporated into DNA strands and inhibits DNA synthesis and repair. Cladribine did not induce gene mutation in bacteria or mammalian cells, but it was clastogenic causing chromosomal damage in mammalian cells *in vitro* at a concentration which was 17-fold above the expected clinical C_{max}. *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 long-term 22-month study with subcutaneous administration in mice and in a short-term 26-week study by oral route in transgenic mice.

- In the long-term carcinogenicity study in mice, the highest dose used was 10 mg/kg, which was seen to be genotoxic in the mouse micronucleus study (equivalent to approximately 16-fold the expected human exposure in AUC in patients taking the maximum daily dose of 20 mg cladribine). No increased incidence of lymphoproliferative disorders or other tumour types (apart from Harderian gland tumours, predominantly adenomas) was seen in mice. Harderian gland tumours are not considered to be of clinical relevance, as humans do not have comparable anatomical structures.
- In the short-term carcinogenicity study in Tg rasH2 mice, no cladribine-related increase in incidence of lymphoproliferative disorders or other tumour types was seen at any dose tested up to 30 mg/kg per day (equivalent to approximately 25-fold the expected human exposure in AUC in patients taking the maximum daily dose of 20 mg cladribine).

Cladribine was also assessed in a 1-year monkey study by the subcutaneous route. No increased incidence in lymphoproliferative disorders and no tumours were seen in this study.

Although cladribine may have a potential for genotoxicity, long-term data in mice and monkeys did not provide any evidence of a relevant increased carcinogenicity risk in humans.

Reproduction toxicity

While there were no effects on female fertility, reproductive function or general performance of offspring, cladribine was shown to be embryolethal when administered to pregnant mice, and the compound was teratogenic in mice (also following treatment of the males only) and rabbits. The observed embryolethal and teratogenic effects are consistent with the pharmacologic mechanisms of cladribine. In a male mouse fertility study, malformed foetuses with agenesis of portions of appendage(s) distal the humerus and/or femur were seen. The incidence of affected mouse foetuses in this study was in the same range of spontaneous incidence of amelia and phocomelia in this strain of mice. However, considering cladribine genotoxicity, male-mediated effects related to potential genetic alteration of differentiating sperm cells cannot be excluded.

Cladribine did not affect the fertility of male mice, but observed testicular effects were reduced testicular weights and increased numbers of non-motile sperm. Testicular degeneration and reversible decrease in spermatozoa with rapid progressive motility were also seen in the monkey. Histologically, testicular degeneration was only seen in one male monkey in a 1-year subcutaneous toxicity study.

5. PHARMACEUTICAL PARTICULARS

5.1 List of Excipients

Hydroxypropylbetadex (2 hydroxypropyl-ß cyclodextrin)
Sorbitol
Magnesium stearate

5.2 Shelf-life

The expiry date is indicated in the packaging.

5.3 Special Precautions for Storage

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

5.4 Nature and Content of Container

Oriented polyamide (OPA)/aluminium (Al)/polyvinyl chloride (PVC) – aluminium (Al) blister sealed in a cardboard wallet and fixed in a child-resistant outer carton.

5.5 Package Quantities and Registration Number

MAVENCLAD® 10 mg, Box, 1 blister @ 1 tablet Reg. No. DKI2358502010A1

HARUS DENGAN RESEP DOKTER

Manufactured and primary packed by
NerPharMa S.R.L., Milan, Italy or
R-Pharm Germany GmbH, Illertissen, Germany

Released and secondary packed by
R-Pharm Germany GmbH, Illertissen, Germany

For
Merck Europe B.V., Amsterdam, The Netherlands

Registered and imported by
PT Merck Tbk, Jakarta, Indonesia

SmPC based on CCDS version 11.0 & 12.0
Date of BPOM approval for the update: DD Month YYYY

INFORMASI UNTUK PASIEN

MAVENCLAD®
Cladribine

Baca petunjuk ini dengan hati-hati sebelum mulai minum obat ini.
- Simpan lembar petunjuk ini, Anda mungkin akan memerlukannya kembali.
- Jika Anda mempunyai pertanyaan, harap menghubungi dokter atau apoteker.
- Obat ini diresepkan hanya untuk Anda, jangan diberikan kepada orang lain karena dapat membahayakan orang tersebut meskipun terdapat gejala orang tersebut sama dengan Anda.
- Jika ada efek samping yang serius atau Anda menemukan efek samping yang tidak terdapat pada petunjuk ini, harap hubungi dokter atau apoteker.

Petunjuk ini terdiri dari informasi sebagai berikut:

1 Apa yang dimaksud dengan MAVENCLAD dan apa kegunaannya

MAVENCLAD mengandung zat aktif cladribine, senyawa sitotoksik (membunuh sel) yang sebagian besar bekerja pada limfosit, sel yang terlibat dalam reaksi inflamasi atau peradangan pada sistem kekebalan tubuh.

MAVENCLAD adalah obat yang digunakan untuk mengobati *relapsing-remitting* ***multiple sclerosis*** (MS) pada **orang dewasa**. MS adalah penyakit di mana peradangan menghancurkan selubung pelindung di sekitar saraf.

Pengobatan dengan MAVENCLAD telah terbukti mengurangi munculnya gejala dan memperlambat perkembangan kecacatan fungsi tubuh.

2 Apa yang perlu Anda ketahui sebelum Anda minum MAVENCLAD

Jangan minum obat ini jika Anda:
- **alergi** terhadap **cladribine** atau **salah satu dari bahan-bahan** yang terdapat dalam formula obat ini (lihat bagian *6 Isi dari kemasan dan informasi lain*).
- **HIV positif**, yaitu Anda terinfeksi oleh *human immunodeficiency virus* (HIV).
- sedang menderita tuberkulosis atau hepatitits (peradangan hati).
- dalam keadaan **sistem kekebalan tubuh** melemah karena kondisi medis atau karena **sedang dalam pengobatan lain yang melemahkan sistem kekebalan tubuh** atau menurunkan kemampuan sumsum tulang memproduksi sel darah. Pengobatan yang dimaksud termasuk:
  - ciclosporin, cyclophosphamide, dan azathioprine (digunakan untuk menekan sistem kekebalan, misalnya setelah transplantasi organ)
  - methotrexate (digunakan untuk mengobati psoriasis atau rheumatoid arthritis)
  - kortikosteroid dalam jangka panjang (digunakan untuk mengurangi peradangan, contohnya dalam pengobatan asma).

  Lihat juga 'Obat Lain dan MAVENCLAD'.
- sedang menderita kanker.
- memiliki **gangguan fungsi ginjal sedang atau berat**.
- sedang **hamil** atau menyusui (lihat juga 'Kehamilan dan Menyusui').

Jika tidak yakin kondisi di atas berlaku atau tidak terhadap Anda, **jangan** minum MAVENCLAD dan konsultasikan terlebih dahulu dengan dokter atau apoteker.

Peringatan dan Pencegahan
Konsultasikan kepada dokter atau apoteker sebelum menggunakan MAVENCLAD.

Tes Darah
Anda akan menjalani tes darah sebelum memulai pengobatan untuk memastikan bahwa Anda dapat menggunakan MAVENCLAD. Dokter juga akan melakukan tes darah selama dan setelah pengobatan untuk memastikan bahwa Anda dapat terus menggunakan MAVENCLAD, dan untuk memastikan bahwa Anda tidak mengalami komplikasi apa pun dari pengobatan tersebut.

Infeksi
Anda akan diuji untuk melihat apakah Anda memiliki infeksi sebelum memulai pengobatan MAVENCLAD. Penting untuk menyampaikan kepada dokter jika Anda merasa memiliki infeksi. Gejala infeksi dapat meliputi: demam, nyeri, nyeri otot, sakit kepala, merasa tidak enak badan secara umum, atau mata menguning.

Dokter Anda mungkin dapat menunda atau menghentikan pengobatan terlebih dahulu sampai infeksi sembuh.

Shingles/herpes zoster
Jika perlu, Anda akan divaksinasi herpes zoster sebelum memulai pengobatan. Anda harus menunggu antara 4 dan 6 minggu agar vaksinasi bekerja**. Segera beri tahu dokter jika Anda mengalami gejala herpes zoster**, komplikasi umum MAVENCLAD (lihat bagian *4 Efek samping yang mungkin terjadi*), yang mungkin memerlukan perawatan khusus.

Progressive multifocal leukoencephalopathy (PML)
Jika Anda merasa **MS Anda semakin parah** atau jika Anda **sadar akan mulai mengalami gejala baru**, misalnya perubahan suasana hati atau perilaku, ingatan menghilang, kesulitan bicara dan komunikasi, segera hubungi dokter. Hal tersebut dimungkinkan gejala gangguan otak langka yang disebabkan oleh infeksi dan disebut leukoensefalopati multifokal progresif/*progressive multifocal leukoencephalopathy* (PML). PML adalah kondisi serius yang dapat menyebabkan kecacatan parah atau kematian.

Meskipun efek PML belum pernah diamati dengan MAVENCLAD, sebagai tindakan pencegahan, Anda mungkin memerlukan pemeriksaan MRI (*magnetic resonance imaging*/pencitraan resonansi magnetik) kepala sebelum memulai perawatan.

Kanker
Kejadian tunggal kanker telah teramati pada pasien yang telah menerima cladribine dalam studi klinis.

Bicarakan dengan dokter jika Anda sebelumnya menderita kanker. Dokter akan memutuskan pilihan pengobatan terbaik untuk Anda. Sebagai tindakan pencegahan, Anda harus mengikuti rekomendasi skrining kanker standar, sebagaimana yang disarankan oleh dokter Anda.

Gangguan Hati
MAVENCLAD dapat menyebabkan gangguan hati. **Bicarakan dengan dokter sebelum minum MAVENCLAD jika Anda sedang atau pernah memiliki gangguan hati. Sampaikan kepada dokter jika Anda merasakan salah satu atau lebih gejala berikut:** merasa sakit (mual), muntah, sakit perut,

kelelahan (letih), kehilangan nafsu makan, kulit atau mata kuning (sakit kuning), atau urin berwarna gelap. Hal tersebut bisa menjadi gejala gangguan hati yang serius.

Konstrasepsi
Pria dan wanita harus menggunakan metode kontrasepsi yang efektif selama pengobatan MAVENCLAD dan setidaknya 6 bulan setelah dosis terakhir. Hal ini penting karena MAVENCLAD dapat secara serius membahayakan bayi Anda.

Lihat juga 'Kehamilan dan Menyusui'.

Transfusi Darah
Jika Anda memerlukan transfusi darah, beri tahu dokter jika Anda menggunakan MAVENCLAD. Anda mungkin harus menjalani iradiasi darah untuk mencegah komplikasi.

Perubahan Pengobatan
Jika Anda beralih dari obat MS lainnya ke MAVENCLAD, dokter Anda akan memeriksa apakah jumlah sel darah (limfosit) Anda normal sebelum Anda memulai pengobatan.

Jika Anda beralih dari MAVENCLAD ke obat MS lainnya, bicarakan dengan dokter Anda. Mungkin terdapat efek tumpang tindih terhadap sistem kekebalan Anda.

Anak-anak dan Remaja
Penggunaan MAVENCLAD tidak dianjurkan pada pasien di bawah usia 18 tahun, karena belum diteliti pada kelompok usia ini.

Obat Lain dan MAVENCLAD
Konsultasikan ke dokter atau apoteker jika Anda sedang, baru saja, atau akan menggunakan obat lain.

Jangan memulai MAVENCLAD bersamaan dengan obat-obatan yang melemahkan sistem kekebalan tubuh atau mengurangi produksi sel darah oleh sumsum tulang. Obat tersebut termasuk:
- ciclosporin, cyclophosphamide, dan azathioprine (digunakan untuk menekan sistem kekebalan, misalnya setelah transplantasi organ)
- methotrexate (digunakan untuk mengobati psoriasis atau rheumatoid arthritis)
- kortikosteroid dalam jangka panjang (digunakan untuk mengurangi peradangan, contohnya dalam pengobatan asma). Kortikosteroid jangka pendek dapat digunakan bila disarankan dokter Anda.

Jangan menggunakan MAVENCLAD bersamaan dengan obat untuk MS lainnya kecuali secara khusus disarankan oleh dokter Anda. Obat lainnya tersebut termasuk alemtuzumab, daclizumab, dimethyl fumarate, fingolimod, glatiramer acetate, interferon beta, natalizumab, atau teriflunomide.

Jangan minum MAVENCLAD bersamaan dengan obat lain. Beri jarak minimal 3 jam antara minum MAVENCLAD dan minum obat lain. MAVENCLAD mengandung hydroxypropylbetadex yang dapat berinteraksi dengan obat lain dalam perut Anda.

Bicarakan dengan dokter jika Anda sedang atau pernah diobati dengan:
- obat-obatan yang dapat mempengaruhi sel darah Anda (contohnya carbamazepine, digunakan untuk pengobatan epilepsi). Dokter mungkin perlu mengawasi Anda lebih ketat.
- jenis vaksin tertentu (vaksin hidup dan vaksin hidup yang dilemahkan). Jika Anda telah divaksinasi dalam 4 hingga 6 minggu terakhir, terapi MAVENCLAD harus ditunda. Anda tidak boleh menerima vaksin tersebut selama perawatan MAVENCLAD. Sistem kekebalan Anda harus pulih sebelum Anda dapat divaksinasi, dan dipastikan dengan tes darah.
- dilazep, nifedipine, nimodipine, reserpine, cilostazol, atau sulindac (digunakan untuk mengobati penyakit jantung, tekanan darah tinggi, kondisi pembuluh darah atau peradangan), atau eltrombopag

(digunakan untuk mengobati kondisi yang berhubungan dengan perdarahan). Dokter akan memberi tahu apa yang harus dilakukan jika Anda memang harus minum obat ini.
- rifampicin (digunakan untuk mengobati jenis infeksi tertentu), St. John's wort (digunakan untuk mengobati depresi) atau kortikosteroid (digunakan untuk mengobati peradangan). Dokter akan memberi tahu apa yang harus dilakukan jika Anda memang harus minum obat ini.

Bicarakan kepada dokter jika Anda menggunakan kontrasepsi hormonal (misalnya 'pil KB'). Anda memerlukan metode kontrasepsi non-hormonal selama pengobatan MAVENCLAD dan setidaknya 4 minggu setelah dosis terakhir.

Hamil dan Menyusui
Jangan minum MAVENCLAD jika Anda sedang hamil atau merencanakan kehamilan. Hal ini penting karena MAVENCLAD dapat secara serius membahayakan bayi Anda.

Anda harus menggunakan **metode kontrasepsi yang efektif** untuk mencegah kehamilan selama pengobatan MAVENCLAD dan setidaknya 6 bulan setelah dosis terakhir. **Bicarakan kepada dokter** jika Anda menggunakan kontrasepsi hormonal (misalnya 'pil KB'). Anda memerlukan metode kontrasepsi non-hormonal selama pengobatan MAVENCLAD dan setidaknya 4 minggu setelah dosis terakhir. Jika Anda hamil lebih dari 6 bulan setelah dosis terakhir di tahun 1, diperkirakan tidak ada risiko keamanan yang terjadi namun artinya Anda tidak dapat menerima pengobatan dengan MAVENCLAD selama masa kehamilan ini.

Jika Anda adalah pria, Anda harus menggunakan metode kontrasepsi yang efektif untuk mencegah pasangan Anda hamil, selama Anda dalam pengobatan dengan MAVENCLAD dan hingga 6 bulan setelah dosis terakhir.

Dokter akan memberikan panduan tentang metode kontrasepsi yang tepat.

Jangan minum MAVENCLAD jika Anda sedang menyusui. Jika pertimbangan dokter meyakini bahwa MAVENCLAD sangat penting untuk Anda, dokter akan menyarankan Anda untuk berhenti menyusui.

Mengendarai Kendaraan atau Mengoperasikan Mesin
MAVENCLAD tidak mempengaruhi kemampuan mengendarai kendaraan atau mengoperasikan mesin Anda.

MAVENCLAD Mengandung Sorbitol
Obat ini mengandung 64 mg sorbitol dalam setiap tabletnya.

3 Bagaimana meminum MAVENCLAD

Selalu minum obat ini sesuai dengan anjuran dokter. Anda harus cek ke dokter maupun apoteker apabila Anda belum yakin.

Jangka Siklus Pengobatan (*Course* Pengobatan)
Anda akan diberikan MAVENCLAD dalam **dua *course* pengobatan** selama **2 tahun**.
Setiap *course* perawatan terdiri dari **2 minggu perawatan**, yang berjarak satu bulan di awal setiap tahun perawatan.
Seminggu pengobatan terdiri dari **4 atau 5 hari di mana Anda menerima 1 atau 2 tablet setiap hari (lihat Tabel 1)**.

Contoh: jika Anda memulai pengobatan pada pertengahan April, Anda minum tablet seperti berikut.

Tabel 1

Tahun 1	Tahun 2

Minggu pengobatan pertama	Pertengahan April: 1 atau 2 tablet setiap hari untuk 4 atau 5 hari	Minggu pengobatan pertama	Pertengahan April: 1 atau 2 tablet setiap hari untuk 4 atau 5 hari
Minggu pengobatan kedua	Pertengahan Mei: 1 atau 2 tablet setiap hari untuk 4 atau 5 hari	Minggu pengobatan kedua	Pertengahan Mei: 1 atau 2 tablet setiap hari untuk 4 atau 5 hari

Sebelum Anda memulai *course* pengobatan, dokter akan melakukan tes darah untuk memeriksa apakah kadar limfosit (sejenis sel darah putih) berada dalam kisaran yang dapat diterima. Jika kadar limfosit di luar kisaran tersebut, pengobatan Anda akan ditunda.

Setelah Anda menyelesaikan 2 *course* pengobatan selama 2 tahun, dokter akan terus memantau kesehatan Anda selama 2 tahun lagi, di mana Anda tidak perlu minum obat lagi.

Dosis

1. Anda akan diresepkan jumlah tablet yang tepat untuk setiap minggu pengobatan, berdasarkan berat badan seperti yang ditunjukkan pada Tabel 2.
2. Anda akan membutuhkan satu atau beberapa kemasan obat untuk memperoleh jumlah tablet yang tepat.
3. Ketika menerima persediaan obat Anda, periksa apakah Anda mendapatkan jumlah tablet yang benar.
4. Di kolom kiri tabel di bawah, temukan baris yang sesuai dengan berat badan Anda (dalam kg), lalu periksa jumlah tablet yang harus tersedia dalam kemasan untuk minggu pengobatan yang akan Anda mulai.
5. Jika jumlah tablet dalam kemasan Anda berbeda dari jumlah yang tertera untuk berat badan Anda pada tabel di bawah, sampaikan ke dokter.
6. Perhatikan bahwa untuk beberapa kisaran berat badan, jumlah tablet dapat bervariasi dari satu minggu perawatan ke minggu berikutnya.

Misal: jika berat badan Anda 85 kg dan akan memulai pengobatan minggu 1, Anda akan diberikan 8 tablet.

Tabel 2

Berat Badan Anda	**Jumlah tablet yang harus diminum**			
	Course pengobatan Tahun 1		Year 2 treatment course	
	Pengobatan minggu 1	Pengobatan minggu 2	Pengobatan minggu 1	Pengobatan minggu 2
Kurang dari 40 kg	Dokter akan memberi tahu Anda jumlah tablet yang harus diminum			
40 hingga kurang dari 50 kg	4	4	4	4
50 hingga kurang dari 60 kg	5	5	5	5
60 hingga kurang dari 70 kg	6	6	6	6
70 hingga kurang dari 80 kg	7	7	7	7
80 hingga kurang dari 90 kg	8	7	8	7
90 hingga kurang dari 100 kg	9	8	9	8
100 hingga kurang dari 110 kg	10	9	10	9
110 kg dan lebih ke atas	10	10	10	10

Bagaimana Meminum Obat Anda

Minumlah tablet pada waktu yang hampir sama setiap harinya. Telan tablet tanpa dikunyah. Anda tidak harus minum tablet pada waktu makan. Anda dapat meminumnya dengan makanan atau di antara waktu makan.

Baca 'Panduan Langkah-Langkah' di akhir brosur ini tentang cara membuka *child-resistant packaging* (kemasan tahan anak-anak) dan cara minum tablet yang disertakan dalam kemasan.

Penting
- Pastikan tangan Anda kering sebelum mengambil tablet dari kemasannya.
- Tekan tablet dari blister dan segera telan.
- Jangan biarkan tablet Anda terlalu lama terbuka di luar, misalnya di atas meja, atau memegang tablet terlalu lama.
- Jika tablet tertinggal di suatu permukaan atau jika pecah dan serpihan jatuh dari blister, area tersebut harus dicuci bersih.
- Cuci tangan Anda dengan menyeluruh setelah memegang tablet.
- Jika Anda kehilangan tablet, hubungi dokter Anda untuk meminta nasihat.

Durasi dari Satu Minggu Pengobatan
Tergantung dari jumlah total tablet yang diresepkan untuk Anda, Anda harus meminumnya selama 4 atau 5 hari, dalam setiap minggu pengobatan.

Tabel 3 menunjukkan berapa banyak tablet (1 atau 2 tablet) yang harus Anda minum setiap hari. Jika dosis harian Anda adalah 2 tablet, minumlah secara bersamaan.

Contoh: jika Anda harus minum 8 tablet, Anda akan minum 2 tablet pada Hari 1, Hari 2, Hari 3, lalu 1 tablet pada Hari 4 dan Hari 5.

Tabel 3

Jumlah total tablet per minggu pengobatan	Hari 1	Hari 2	Hari 3	Hari 4	Hari 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

Jika Anda Minum MAVENCLAD Lebih dari Seharusnya
Jika Anda telah meminum lebih banyak tablet dari yang seharusnya, segera hubungi dokter Anda. Dokter akan memutuskan apakah Anda perlu menghentikan pengobatan atau tidak.

Terdapat pengalaman terbatas mengenain overdosis MAVENCLAD. Diketahui bahwa semakin banyak obat yang Anda minum, semakin sedikit kadar limfosit dalam tubuh Anda, yang mengakibatkan limfopenia (lihat bagian *4 Efek samping yang mungkin terjadi*).

Jika Anda Lupa Minum MAVENCLAD

Jika melewatkan satu dosis dan ingat pada hari yang sama Anda seharusnya meminumnya	**Jika Anda melewatkan satu dosis dan tidak mengingatnya sampai hari berikutnya**
Minum dosis yang terlewat pada hari itu.	Jangan minum dosis yang terlewat bersama dengan dosis terjadwal berikutnya.

	Minum dosis yang terlewat pada hari berikutnya dan perpanjang jumlah hari dalam minggu perawatan tersebut.

Contoh: Jika Anda lupa minum dosis Hari 3 dan tidak mengingatnya sampai Hari 4, minum dosis Hari 3 pada Hari 4, dan perpanjang jumlah hari dalam minggu perawatan menjadi ditambah 1 hari. Jika Anda melewatkan 2 dosis berturut-turut (misalnya dosis Hari 3 dan Hari 4), minum dosis yang terlewat untuk masing-masing 2 hari berikutnya, dan kemudian perpanjang minggu pengobatan ditambah 2 hari.

Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan kepada dokter atau apoteker.

4 Efek samping yang mungkin terjadi

Seperti halnya obat lain, obat ini dapat menyebabkan efek samping, meskipun tidak semua pasien mengalaminya. **Beberapa efek dapat terjadi atau dapat menjadi berat.**

Limfopenia dan *Shingles*/herpes zoster
Efek samping yang paling signifikan adalah pengurangan jumlah sel darah putih yang disebut limfosit (**limfopenia**), yang sangat umum terjadi (dapat mempengaruhi lebih dari 1 dari 10 orang) dan mungkin berat.
Limfopenia dapat meningkatkan risiko terkena infeksi. Infeksi yang biasa terlihat dengan penggunaan MAVENCLAD adalah **herpes zoster**.

Segera beri tahu dokter jika Anda memiliki gejala herpes zoster seperti 'pita' yang terasa sangat nyeri dan ruam yang melepuh, biasanya di satu sisi tubuh bagian atas atau wajah. Gejala lain dapat berupa sakit kepala, terbakar, kesemutan, mati rasa atau gatal-gatal pada kulit di daerah yang terkena, merasa tidak sehat atau demam pada tahap awal infeksi.

Herpes zoster perlu diobati, dan pengobatan MAVENCLAD mungkin perlu dihentikan sementara sampai infeksi sembuh.

Gangguan hati (tidak umum terjadi – dapat terjadi pada ≥1/1,000 hingga <1/100)

Segera hubungi dokter jika Anda merasakan gejala seperti merasa sakit (mual), muntah, sakit perut, kelelahan (letih), kehilangan nafsu makan, kulit atau mata kuning (sakit kuning), atau urin berwarna gelap

Efek Samping Lainnya yang Dapat Terjadi
Efek samping yang umum terjadi (dapat terjadi pada ≥1/100 hingga <1/10 pasien)
- Herpes simpleks (herpes pada mulut)
- Ruam
- Rambut rontok
- Penurunan jumlah sel darah putih tertentu (neutrofil)
- Reaksi alergi, termasuk gatal-gatal, ruam, dan pembengkakan pada bibir, lidah, dan wajah

Efek samping yang sangat jarang terjadi (dapat terjadi pada <1/10.000 pasien)
- Tuberkulosis

Pelaporan efek samping
Jika Anda mengalami efek samping, beritahukan dokter atau apoteker Anda. Hal ini termasuk untuk efek samping yang tidak tercantum dalam petunjuk ini. Anda juga dapat melaporkan keluhan efek samping tersebut ke PT Merck Tbk melalui email ICSR_SEA@merckgroup.com. Dengan melaporkan efek samping, Anda dapat membantu untuk memberikan informasi lebih lengkap terkait dengan keamanan obat ini.

5 Bagaimana menyimpan MAVENCLAD

Simpan obat ini jauh dari jangkauan anak-anak.

Jangan gunakan obat ini setelah masa kedaluwarsa yang tertera setelah tulisan EXP pada kemasan berakhir. Tanggal kedaluwarsa adalah hari terakhir pada bulan yang tertera.

Simpan pada kemasan aslinya untuk melindung obat dari kelembaban.

Jangan membuang obat ini melalui saluran pembuangan air atau limbah rumah tangga. Tanyakan kepada apoteker bagaimana membuang obat-obatan yang tidak diperlukan. Hal ini untuk menjaga lingkungan.

6 Isi dari kemasan dan informasi lain

Apa kandungan MAVENCLAD

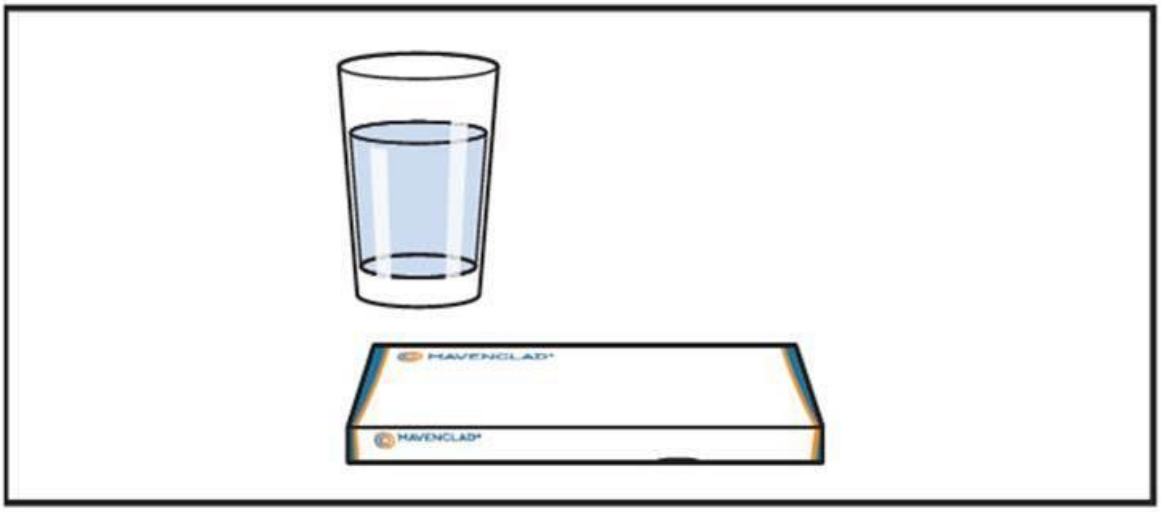
- Zat aktifnya adalah cladribine. Setiap tabletnya mengandung 10 mg cladribine.
- Bahan lainnya adalah hydroxypropylbetadex, sorbitol, dan magnesium stearate.

Bagaimana bentuk MAVENCLAD dan isi dari kemasan

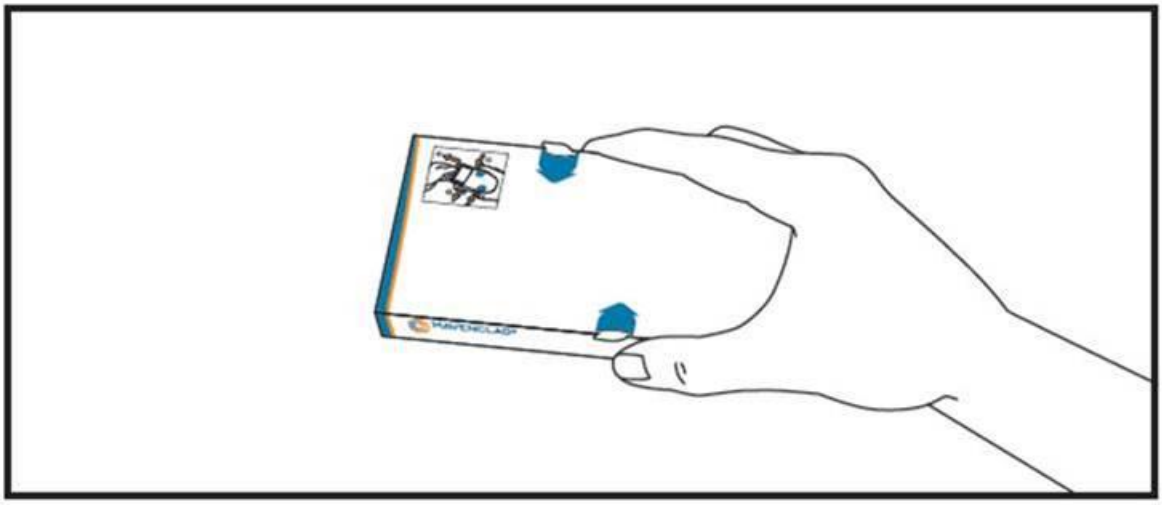
Tablet MAVENCLAD berwarna putih, bentuk bulat, tablet cembung dengan tercetak ‘C’ di salah satu sisi dan ‘10’ di sisi lainnya. Setiap kemasan dus berisi 1 tablet dalam blister, disegel dalam dompet karton dan dipasang dalam kemasan dus tahan anak-anak (*child-resistant packaging*).

Panduan Langkah-Langkah Minum Tablet MAVENCLAD 10 mg

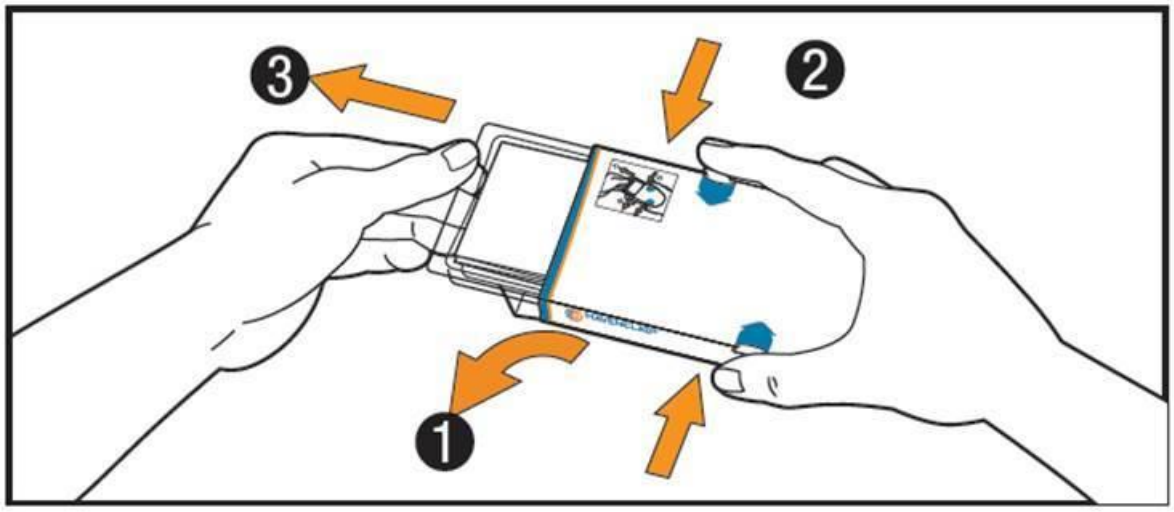
MAVENCLAD dikemas dalam kemasan dus tahan anak-anak (*child-resistant packaging*) yang dapat ditutup kembali dan harus dijauhkan dari jangkauan anak-anak. Baca informasi di bawah untuk panduan langkah demi langkah cara membuka kemasan dan cara minum tablet MAVENCLAD.



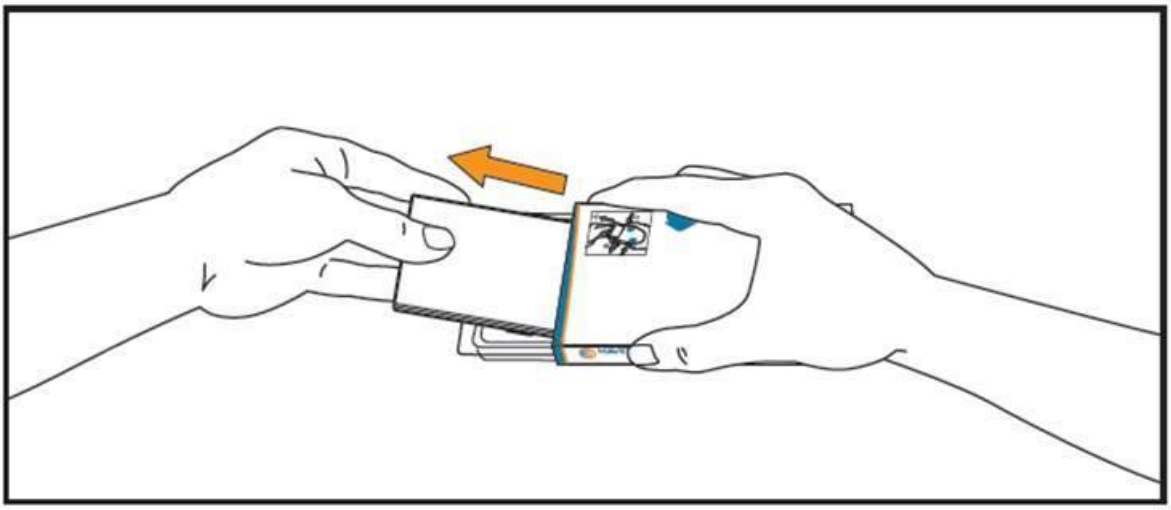
1. Siapkan segelas air putih dan pastikan tangan Anda bersih dan kering sebelum membuka tablet.



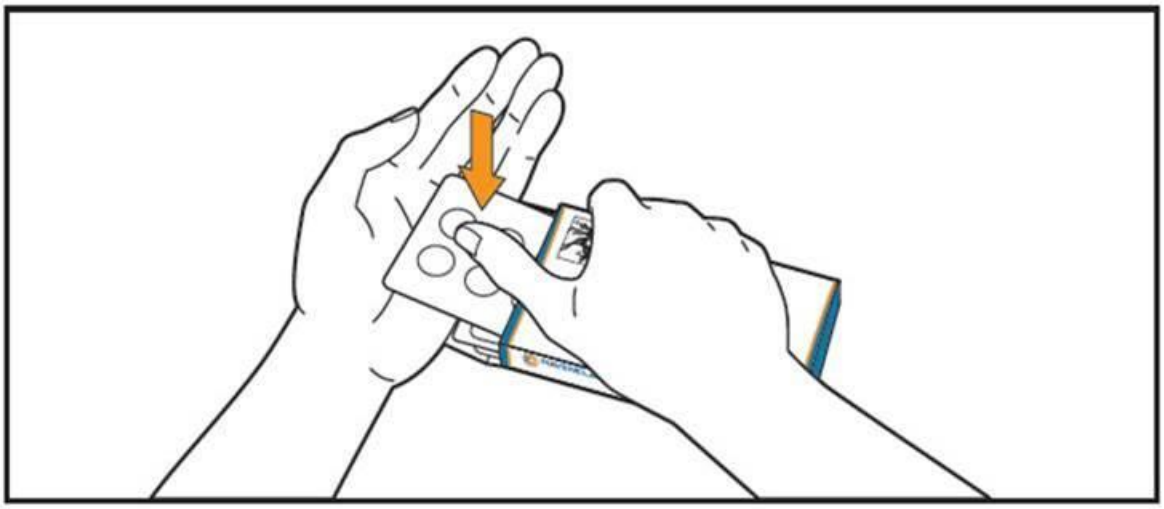
2. Pegang kemasan dus dengan sisi petunjuk membuka kemasan menghadap ke atas.



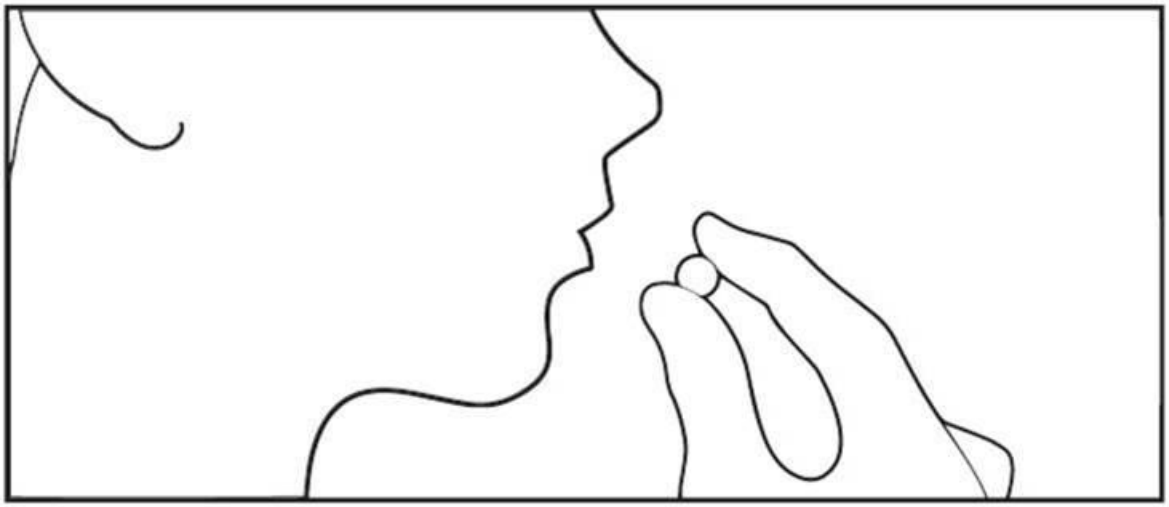
3. (1) Buka tutup kemasan pada ujung sebelah kiri.
   (2) Tekan kait di kedua sisi kemasan secara bersamaan menggunakan jari telunjuk dan ibu jari Anda, kemudian tahan pengait tersebut.
   (3) Tarik keluar *tray* (baki) hingga terhenti. **Perhatian:** Jangan lepas *tray* (baki) dari dus kemasan.



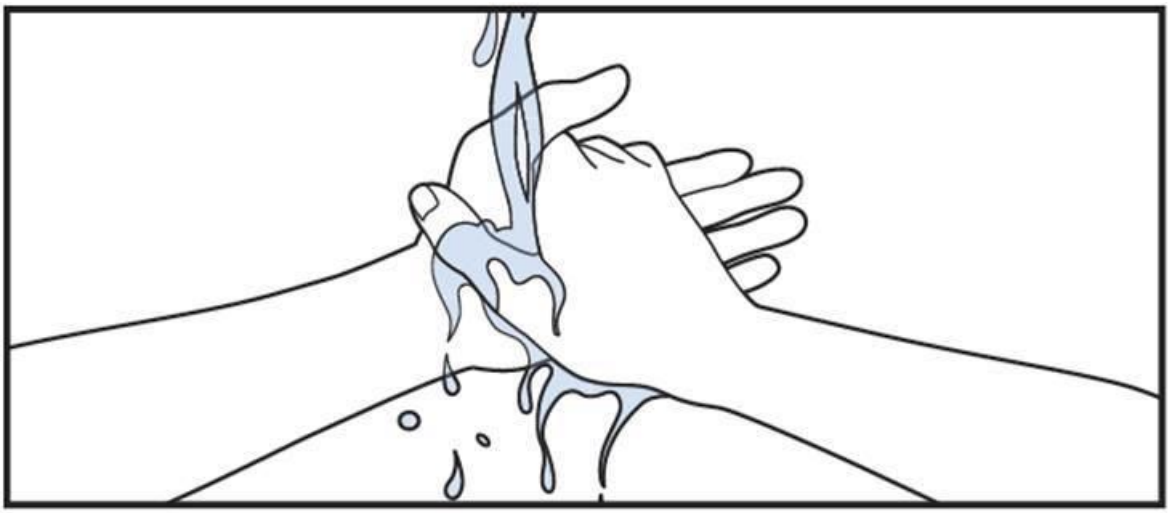
4. Ambil brosur dari *tray* (baki). Pastikan Anda telah membaca semua isi brosur termasuk panduan langkah demi langkah dan menyimpannya di tempat yang aman.



5. Naikkan kemasan blister menggunakan jari Anda melalui lubang di *tray* (baki). Letakkan telapak tangan Anda di bawah kemasan blister dan dorong 1 tablet ke telapak tangan Anda, sesuai dengan dosis yang diresepkan.



6. Telan tablet dengan air putih. Tablet harus ditelan secara utuh dan tidak dikunyah atau dibiarkan larut di mulut Anda. Kontak dengan kulit harus dibatasi. Hindari langsung menyentuh hidung, mata, dan bagian tubuh lainnya.



7. Cuci tangan Anda secara menyeluruh dengan sabun dan air.

Jangan mengeluarkan tablet dari blister jika belum akan segera diminum. Jangan menyimpan tablet dalam wadah selain kemasan aslinya.

Kemasan dan Nomor Izin Edar
MAVENCLAD® 10 mg, Dus, 1 blister @ 1 tablet Reg. No. DKI2358502010A1

HARUS DENGAN RESEP DOKTER

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