MAVENCLAD® Tablet 10mg

1. NAME OF THE MEDICINAL PRODUCT

MAVENCLAD® 10 mg tablets

2. 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 6.1.

3. PHARMACEUTICAL FORM

Tablet.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MAVENCLAD® is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults. Because of its safety profile, use of MAVENCLAD® is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of MS.

Limitations of Use

MAVENCLAD® is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile

4.2 Posology and method of administration

Treatment must be initiated and supervised by a physician experienced in the treatment of MS.

Posology

The recommended cumulative dose 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 (eg, 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 5.1). Re-initiation of therapy after year 4 has not been studied.

Criteria for initiating and continuing therapy

Lymphocyte counts must be
- normal before initiating treatment in year 1,
- at least 800 cells/mm³ before initiating treatment 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 cladribine tablets 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 cladribine per treatment week by patient weight in each treatment year

Weight range	Dose in mg (number of 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 Number of 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 4.5).

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 5.2).

Safety and efficacy in patients with moderate or severe renal impairment have not been established. Therefore, cladribine is contraindicated in these patients (see section 4.3).

Hepatic impairment

No studies have been conducted in patients with hepatic impairment.

No dose adjustment is required in patients with mild hepatic impairment because the importance of hepatic function for the elimination of cladribine is considered negligible (see Pharmacokineitc properties). In the absence of data, the use of cladribine is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh score >6).

Elderly

Caution is recommended when cladribine 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 cladribine in children 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 longer 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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 4.5).

Active malignancy.

Moderate or severe renal impairment (creatinine clearance <60 mL/min) (see section 5.2).

Pregnancy and breast-feeding (see section 4.6).

4.4 Special warnings and 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 4.5).

Lymphocyte counts must be determined

- before initiating treatment in year 1,
- before initiating treatment 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 4.2 and subsection 'Infections' below.

Infections

Cladribine can reduce the body's immune defence and may increase the likelihood of infections. Serious, severe, and opportunistic infections – including events with fatal outcome – have been observed with Mavenclad treatment. HIV infection, active tuberculosis and active hepatitis must be excluded before initiation of cladribine (see section 4.3).

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 4.8).

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.

Although no case of PML has been reported with cladribine tablets, a baseline magnetic resonance imaging (MRI) should be performed before initiating cladribine tablets treatment (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 4.8).

MAVENCLAD® is contraindicated in MS patients with active malignancies (see section 4.3). An individual benefit-risk evaluation should be performed before initiating treatment in patients with prior malignancy. Patients treated with cladribine 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 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, including unexplained liver enzyme elevations or symptoms suggestive of hepatic dysfunction (e.g., unexplainednausea, 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 4.6).

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 4.5).

Male patients must take precautions to prevent pregnancy of their female partner during cladribine treatment and for at least 3 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 treatment. A potential additive effect on the immune system should also be considered when such medicinal products are used after treatment (see section 4.5).

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

Elderly
Caution is recommended when cladribine 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 dose adjustment is considered necessary (see section 13).
Safety and efficacy in patients with moderate or severe renal impairment have not been established. Therefore, cladribine is contraindicated in these patients (see section 5).

Hepatic impairment

The use of cladribine is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh score >6) (see section 4.2).

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.

4.5 Interaction with other medicinal products and other forms of interaction

This medicinal product 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 4.3).

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

Other disease-modifying medicinal products

The use of cladribine with interferon beta results in an increased risk of lymphopenia. Safety and efficacy of cladribine 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 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

Co-administration of cladribine with oral hormonal contraceptives (ethinylestradiol and levonorgestrel) showed no clinically relevant pharmacokinetic interaction with cladribine. Therefore, concomitant use of cladribine is not expected to decrease the efficacy of hormonal contraceptives (see section 4.6).

4.6 Fertility, 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 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 5.3). Therefore, male patients must take precautions to prevent pregnancy of their partner during cladribine treatment and for at least 3 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 5.3).

MAVENCLAD ® is contraindicated in pregnant women (see section

Breast-feeding

.Limited data from case reports have shown that cladribine is excreted in human milk. The quantity is not yet well established. 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 4.3).

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 5.3).

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 3 months after the last dose (see above).

4.7 Effects on ability to drive and use machines

MAVENCLAD® has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most clinically relevant adverse reactions are lymphopenia (25.6%) and herpes zoster (3.0%). The incidence of herpes zoster was higher during the period of grade 3 or 4 lymphopenia (<500 to 200 cells/mm³ or <200 cells/mm³) compared to the time when the patients were not experiencing grade 3 or 4 lymphopenia (see section 4.4).

Tabulated 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) and
frequency not known (cannot be estimated from the available data)

Infections and infestations

Common: Oral herpes, dermatomal herpes zoster.
Very rare: Tuberculosis (see section 4.4).

Blood and lymphatic system disorders

Very common: Lymphopenia.
Common: Decrease in neutrophil count.

Immune system disorders
Common: Hyprsensitivity* including pruritus urtucaria, 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 4.4) and strict criteria for initiating and continuing cladribine treatment must be followed (see section 4.2).

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 4.4).

Hypersensitivity

In clinical studies of patients treated with a cumulative dose of 3.5 mg/kg oral cladribine, hypersensitivity events 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 {Tradename}. 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 4.4).

Reporting of suspected adverse reactions after authroisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

There is limited experience with overdose of oral cladribine. Lymphopenia is known to be dose-dependent (see sections 4.4 and 4.8).

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, 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/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 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 4.2).

Efficacy in patients with high disease activity

Post-hoc subgroup efficacy analyses have been conducted in patients with high disease activity treated with oral cladribine at the recommended 3.5 mg/kg cumulative dose. These included

- patients with 1 relapse in the previous year and at least 1 T1 Gd+ lesion or 9 or more T2 lesions, while on therapy with other DMDs,
- patients with 2 or more relapses in the previous year, whether on DMD treatment or not.

In the analyses of the CLARITY data, a consistent treatment effect on relapses was observed with the annualised relapse rate ranging from 0.16 to 0.18 in the cladribine groups and 0.47 to 0.50 in the placebo group ($p < 0.0001$). Compared to the overall population, a greater effect was observed in time to 6-month sustained disability where cladribine reduced the risk of disability progression by 82% (hazard ratio = 0.18, 95% CI [0.07, 0.47]). For placebo the 10^{th} percentile for disability progression was reached between 16 and 23 weeks, while for the cladribine groups it was not reached during the entire study.

Secondary progressive MS with relapses

A supportive study in patients treated with cladribine as an add-on to interferon beta vs. placebo + interferon beta also included a limited number of patients with secondary progressive MS (26 patients). In these patients, treatment with cladribine 3.5 mg/kg resulted in a reduction of the annualised relapse rate compared to placebo (0.03 *versus* 0.30, risk ratio: 0.11, $p < 0.05$). There was no difference in annualised relapse rate between patients with relapsing-remitting MS and patients with secondary progressive MS with relapses. An effect on disability progression could not be shown in either subgroup.

Patients with secondary progressive MS were excluded in the CLARITY study. However, a post-hoc analysis of a mixed cohort including CLARITY and ONWARD patients, defined by a baseline EDSS score of ≥3.5 as a proxy for secondary progressive MS, showed a similar reduction in annualised relapse rate compared to patients with an EDSS score below 3.

5.2 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.

Renal impairment

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%.

Hepatic impairment

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

Pharmacokinetic interactions

An interaction study in MS patients showed that the bioavailability of 10 mg oral cladribine was not altered when co-administered with pantoprazole.

5.3 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropylbetadex (2-hydroxypropyl-ß-cyclodextrin)
Sorbitol
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

48 months

6.4 Storage condition

Store below 30ºC

6.5 Special precautions for storage

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

6.6 Nature and contents 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.
Pack sizes of 1, 4, 5, 6, 7 or 8 tablets.

Not all pack sizes may be marketed.

6.7 Special precautions for disposal

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

7. MANUFACTURER

NerPharMa S.R.L.

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Italy

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