1 PRODUCT NAME

Merck Cladribine 10 mg tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of Merck Cladribine tablet contains 10 mg cladribine.

The tablets also contain hydroxypropylbetadex, sorbitol and magnesium stearate.

3 PHARMACEUTICAL FORM

Merck Cladribine tablet tablets are uncoated, white, round and biconvex, and engraved with 'C' on one side and '10' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Merck Cladribine tablet is indicated for the treatment of relapsing-remitting multiple sclerosis (RRMS) to reduce the frequency of clinical relapses and to delay the progression of physical disability.

Following completion of the 2 treatment courses, no further cladribine treatment is required in years 3 and 4. Re-initiation of therapy after year 4 has not been studied.

4.2 Dose and method of administration

Dose

General Treatment Schedule

The recommended cumulative dose of Cladribine tablet 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 year. Each treatment week consists of 4 or 5 days on which a patient receives 10 mg or 20 mg (one or two tablets) as a single daily dose, depending on body weight.

Patients should receive no more than 2 treatment courses over two consecutive years. The recommended dose should not be exceeded. Following completion of the 2 treatment courses, no further cladribine treatment is required in year 3 and year 4 (see section 5.1 Pharmacodynamic properties, Clinical trials). Re-initiation of therapy after year 4 has not been studied.

Criteria for Starting and Continuing Therapy

Screening for infections

HIV infection, active tuberculosis and active hepatitis must be excluded before initiation of Merck Cladribine tablet (refer to section 4.3 Contraindications).

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 Merck Cladribine tablet should be delayed until the infection has been adequately treated (refer to section 4.4 Special warnings and precautions for use, Infections).

A delay in initiation of Merck Cladribine tablet should also be considered in patients with an acute infection until the infection is fully controlled (refer to section 4.4 Special warnings and precautions for use, Infections).

Lymphocyte monitoring

Lymphocyte counts must be

- normal before initiating Cladribine tablet therapy,
- at least 800 cells/mm³ before the second treatment course 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 tablet anymore.

Liver function

Serum aminotransferase, alkaline phosphatase, and total bilirubin levels should be obtained prior to initiation of therapy in year 1 and year 2 (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Liver Function).

Distribution of dose

The distribution of the total dose over the 2 years of treatment is provided in Table 1. Note that for some weight ranges the number of tablets may vary from one treatment week to the next.

Table 1: Dose of Merck Cladribine 10 mg tablet 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)

* Use of Cladribine tablet in patients weighing less than 40 kg has not been investigated.

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 tablet 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: Merck Cladribine 10 mg tablets per week day

Total number of tablets per treatment week	Day 1	Day 2	Day 3	Day 4	Day 5
4	1	1	1	1	0
5	1	1	1	1	1
6	2	1	1	1	1

Table 2: Merck Cladribine 10 mg tablets per week day					
Total number of tablets per treatment week	Day 1	Day 2	Day 3	Day 4	Day 5
7	2	2	1	1	1
8	2	2	2	1	1
9	2	2	2	2	1
10	2	2	2	2	2

Dosing Errors

A missed dose can be taken as soon as remembered, if remembered on the same day.

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

In case of an accidental dose higher than prescribed, the clinical status of the patient must be reviewed and a decision made as to whether and how to continue treatment.

Paediatric population

The safety and efficacy of Cladribine tablet in children aged under 18 years old have not been established. The effect of age < 18 years and > 65 years on cladribine pharmacokinetics has not been studied.

Method of Administration

Cladribine tablets must be taken orally, with water, and swallowed without chewing. It is unlikely that food intake will have a clinically significant effect on absorption of cladribine. Therefore, Cladribine tablet can be taken before or after a meal.

As tablets are uncoated, they must be swallowed immediately once removed from the blister and not 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 afterwards.

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

4.3 Contraindications

Cladribine tablet therapy must not be initiated in:

- patients with hypersensitivity to cladribine or to any of the tablet excipients listed in section 6.1 List of excipients.
- patients who are infected with the human immunodeficiency virus (HIV).
- patients with active chronic infections (tuberculosis, hepatitis) (refer to 4.4 Special warnings and precautions for use).
- immunocompromised patients, including patients receiving immunosuppressive or myelosuppressive therapy with agents such as cyclosporin, methotrexate, mitoxantrone,

azathioprine, natalizumab, or chronic use of corticosteroids. Acute short-term therapy with corticosteroids can be administered.
- patients with moderate or severe renal impairment (creatinine clearance < 60 mL/min) (see section 5.2 Pharmacokinetic properties).
- pregnancy and breastfeeding (refer to 4.4 Special warnings and precautions for use, 4.6 Fertility, pregnancy and lactation).

4.4 Special warnings and precautions for use

Therapy is to be initiated and supervised by neurologists. Neurologists must discuss the risks and benefits of therapy with the patient and explain the importance of following the recommendations in the Consumer Medicine Information, in particular with respect to infections and haematological monitoring. The long term safety of Cladribine tablet has not been assessed. There is no conclusive evidence of an increase in the incidence of malignancies.

Haematological Monitoring

The mode of action of Cladribine tablet 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 the limits of normal.

Lymphocyte counts must be determined:

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

Monitoring of other haematological parameters can be considered at the discretion of the physician.

For treatment decisions based on the patient's lymphocyte count, refer to 4.2 Dose and method of administration and Infections below.

Infections

Cladribine tablet 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 (refer to 4.3 Contraindications).

Latent infections may be activated, including tuberculosis, viral hepatitis or herpes zoster infections. 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 Cladribine tablet 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.

In clinical trials, a fatal case of hepatitis B was observed, but was not considered related to cladribine. Three cases of reactivation of latent tuberculosis, including one fatal case, were observed before implementation of the pre-screening for infections as recommended above. For most common infections, incidence rates were similar between patients receiving cladribine and those receiving placebo, except for herpes zoster.

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 tablet. Initiation of treatment with Cladribine tablet must be postponed for 4 to 6 weeks to allow for the full effect of vaccination to occur (refer to 4.4 Special warnings and precautions for use, Live and live attenuated vaccines).

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 (refer to 4.8 Undesirable effects).

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

In the clinical trial data base of cladribine in MS (1,976 patients, 8,650 patient years) no case of progressive multifocal leukoencephalopathy (PML) has been reported. However, a baseline magnetic resonance imaging (MRI) should be considered before initiating Cladribine tablet (usually within 3 months). This is particularly recommended if patients are switched from other MS agents that have a risk of PML.

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.

Malignancies
In clinical studies and long-term follow-up (mean [±SD] duration: 194 ± 111 weeks) 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 3414 patient-years [0.29 events per 100 patient-years]) compared to patients who received placebo (3 events in 2022 patient-years [0.15 events per 100 patient-years]).

Cladribine tablet has not been studied in MS patients with prior or current malignancies (with the exception of *in situ* basal or squamous cell skin cancer surgically removed without recurrence for at least five years). Therefore, Cladribine tablet is not recommended in MS patients with active malignancy.

As with other immunomodulating therapies, caution should be exercised when initiating Cladribine tablet in patients with prior malignancy. It is currently not known whether oral cladribine confers a higher risk for developing malignancies. Observation over longer treatment periods is required before any effect on the development of malignancies can be determined. An individual benefit-risk evaluation should be performed before initiating Merck Cladribine in patients with prior malignancy. Patients treated with Cladribine tablet should be advised to follow standard cancer screening guidelines.

Malignant events reported during the follow-up or in the extension studies included melanoma and non-melanoma skin cancer. Although a causal relationship has not been established, precautionary measures to monitor and prevent a potential risk of skin cancer are recommended, including regular self-examinations, annual dermatological check-ups, avoiding direct exposure to the sun and using sun protection.

Liver Function

Liver injury, including serious cases, has been reported uncommonly in patients treated with Merck Cladribine, especially in patients with a medical history of abnormal liver tests. Patients should have their serum aminotransferase, alkaline phosphatase, and total bilirubin levels assessed prior to initiation of therapy in year 1 and year 2. (see section 4.2 DOSE AND METHOD OF ADMINISTRATION, Criteria for starting and continuing therapy).

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

Switching to and from Cladribine tablet treatment
In patients who have previously been treated with immunomodulating or immunosuppressive agents, the mode of action and duration of effect of the other product should be considered prior to initiation of Cladribine tablet (refer to 4.2 Dose and method of administration). A potential additive effect on the immune system should also be considered when such agents are used after treatment with Cladribine tablet (refer to 4.5 Interaction with other medicines and other forms of interaction, Haematotoxic, Immunosuppressive and Immunomodulating Agents).

When switching from an MS agent with a risk of PML, a baseline MRI is recommended (refer to Infections above).

Renal Impairment
No dedicated studies have been conducted in patients with renal impairment (refer to 4.3 Contraindications).

The safety profile in patients with mild renal impairment (creatinine clearance 60-89 mL/min) was shown to be similar to that in patients with normal renal function; no dosage adjustment is considered necessary.

In patients with moderate or severe renal impairment (creatinine clearance < 60 mL/min), a decrease in cladribine clearance can be predicted (refer to 5.2 Pharmacokinetic properties). Safety and efficacy in patients with moderate or severe renal impairment have not been established. Therefore, Cladribine tablet is contraindicated in these patients (refer to 4.3 Contraindications).

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

Although the importance of hepatic function for the elimination of cladribine is considered negligible (refer to 5.2 Pharmacokinetic properties), in the absence of data, use of Cladribine tablet is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh score > 6).

Fructose Intolerance
Cladribine tablet contains 64.04 mg sorbitol per tablet. Its use is not recommended in patients with fructose intolerance.

Paediatric Population
Safety and effectiveness of Cladribine tablet in paediatric MS patients are not known. Cladribine tablet is not recommended in patients below the age of 18 years.

Use in the Elderly

Clinical studies with Cladribine tablet did not include patients over 65 years of age to determine whether they respond differently from younger patients.

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

4.5 Interaction with other medicines and other forms of interaction

If any other oral medicines are taken concomitantly, administration must be separated from that of Cladribine tablet by at least 3 hours during the limited number of days of cladribine administration. This is because hydroxypropylbetadex released from Cladribine tablet may lead to complex formation with other agents (especially medicines with low solubility), which could cause an increase in bioavailability of such a product.

Haematotoxic, Immunosuppressive and Immunomodulating Agents

Use of Cladribine tablet in immunocompromised patients, including patients receiving immunosuppressive or myelosuppressive therapy with, e.g. cyclosporin, methotrexate, mitoxantrone, azathioprine, natalizumab, or chronic use of corticosteroids is contraindicated because of a risk of additive effects on immune status (refer to 4.3 Contraindications). Acute short-term therapy with corticosteroids can be administered if clearly necessary.

Safety and efficacy of Cladribine tablet in combination with other disease-modifying treatments for MS has not been assessed. Concomitant treatment is not recommended.

Because of the cladribine-induced reduction in lymphocyte count, additive haematological adverse effects may be expected if Cladribine tablet is administered prior to or concomitantly with other agents that affect the haematological profile (e.g. carbamazepine, non-steroidal anti-inflammatory drugs). Careful monitoring of haematological parameters is recommended in such cases.

The use of Merck Cladribine with interferon-beta results in an increased risk of lymphopenia. This needs to be considered when interferon-beta is used after cladribine.

Live or Live Attenuated Vaccines

Treatment with Cladribine tablet must 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 must be avoided during a Cladribine tablet treatment, as long as the patient's white blood cell counts are not within normal limits.

Potent ENT1, CNT3 and ABCG2 transporter inhibitors

Based on *in vitro* data suggesting inhibition of ENT1, CNT3 or ABCG2 transport proteins, the bioavailability, intracellular distribution and renal elimination of cladribine may theoretically be altered by medicinal products containing potent ENT1, CNT3 and ABCG2 transporter inhibitors, such as dipyridamole, dilazep, nifedipine, nimodipine, cilostazol, sulindac, reserpine or eltrombopag. The net effects in terms of potential cladribine exposure alterations are difficult to predict and hence, the clinical relevance of these findings is unknown.

It is recommended that co-administration of these products be avoided during the 4 to 5 day Cladribine tablet treatment. If this is not possible, selection of alternative concomitant medicinal products with no, or minimal ENT1, CNT3 or ABCG2 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 by several hours, and careful patient monitoring is recommended.

Potent ABCG2 and P-gp transporter inducers

The effects of potent inducers of the efflux transporters ABCG2 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 ABCG2 (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 tablet treatment and for at least 4 weeks after the last dose in each treatment year (refer to 4.6 Fertility, pregnancy and lactation, Use in Pregnancy).

Other

In vitro studies suggest that cladribine efflux is not or only minimally P-gp related. Clinically relevant interactions with inhibitors of P-gp are not expected.

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

Cladribine showed no significant potential to act as inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. Inhibition of one of these enzymes, or genetic polymorphism (e.g. in CYP2D6, CYP2C9 or CYP2C19) is not expected to result in clinically significant effects on Cladribine tablet pharmacokinetics.

Cladribine has no inductive effect on CYP1A2, CYP2B6 and CYP3A4 enzymes.

4.6 Fertility, pregnancy and lactation

Effects on Fertility

The effect of cladribine on human fertility is unknown. Studies in animals have shown reproductive toxicity.

In male mice, cladribine did not affect fertility at subcutaneous doses up to 30 mg/kg per day, but reduced testes weights and increased numbers of non-motile sperm were seen, indicating the presence of testicular effects. For these effects, 5 mg/kg per day was the no-observed-adverse-effect level (NOAEL).

A 1-year subcutaneous study in monkeys reported testicular degeneration, prostatic inflammation, prostatic and seminal vesicle secretion depletion, epididymal hypospermia and increased incidence of degenerated cells, while a 3-month oral and subcutaneous study noted only reduced sperm motility. The estimated exposure (plasma AUC) at the no-effect oral dose (3 mg/kg/day) was 3-fold clinical MS exposure.

In female mice, cladribine did not affect fertility up to a subcutaneous dose of 8 mg/kg per day (higher doses were not tested). The extrapolated daily exposure data (based on plasma AUC) associated with these dose levels in mice exceeded the daily exposure with the oral human dose in MS by at least an order of magnitude.

While there were no effects on female fertility, reproductive function or general performance of offspring, cladribine was shown to be embryolethal in pregnant mice, and the compound was teratogenic in mice and rabbits. A significant increase in foetal variations was observed in mice receiving 1.5 mg/kg/day or greater intravenously during the period of organogenesis, or from early gestation to weaning, and increased resorptions, reduced litter size and increased foetal malformations were observed in mice receiving 3 mg/kg/day. Foetal malformations were observed

in rabbits that received 3 mg/kg/day intravenously during the period of organogenesis. The observed embryolethal and teratogenic effects are consistent with the pharmacological mechanisms of cladribine.

Use in Pregnancy
There are no adequate or well-controlled studies in human pregnancies. A limited amount of data is available from pregnant women exposed to Cladribine tablet prior to conception. No imbalance of adverse pregnancy outcomes between cladribine and placebo has been observed.

Although clinical data from Cladribine tablet did not reveal evidence of teratogenicity in humans, Cladribine tablet has been shown to inhibit DNA synthesis. Other agents that inhibit DNA synthesis (e.g. methotrexate) have been reported to be teratogenic in humans.

Cladribine tablet is contraindicated in pregnant women (refer to 4.3 Contraindications).

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.

Male Patients
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 tablet treatment and for at least 6 months after the last dose. This will allow time for completion of new male reproductive cycles to clear intracellular phosphorylated cladribine from the body.

If the partner of a male patient becomes pregnant during a course of his Cladribine tablet therapy, it is recommended that the partner be informed about the potential hazard to the foetus.

Female patients

In women of childbearing potential, pregnancy must be excluded before the initiation of Cladribine tablet therapy in year 1 and year 2, and prevented by use of reliable contraception during Cladribine tablet treatment and for at least 6 months (6 menstrual cycles) after the last dose. This will allow for the removal of any follicle that may have been exposed to cladribine during or immediately after a course of treatment. Women using systemically acting hormonal contraceptives should add a barrier method during Cladribine tablet treatment and for at least 4 weeks after the last dose in each treatment year (refer to 4.5 Interaction with other medicines and other forms of interaction). Women who become pregnant during therapy with Cladribine tablet tablets should discontinue treatment.

In case of exposure to Cladribine tablet during pregnancy, it is recommended that the patient be informed about the potential hazard to the foetus.

Use in Lactation
It is not known whether cladribine is excreted in human milk. Because many medicines are excreted in human milk and the potential for serious adverse reactions in nursing infants, breast-feeding is contraindicated during treatment with Merck Cladribine. A decision should be made either to discontinue breast-feeding or to discontinue Cladribine tablet, taking into account the importance of Cladribine tablet to the mother (refer to 4.3 Contraindications).

4.7 Effects on ability to drive and use machines

No studies on the effect of Cladribine tablet on the ability to drive or handle machines have been performed.

4.8 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 (refer to 4.4 Special warnings and precautions for use, Haematological Monitoring, Infections). Lymphopenia led to treatment discontinuation in a phase 3 trial (CLARITY trial) in approximately 2.2% of patients. 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.

Clinical Trials

The safety data described below reflect exposure of 884 patients with MS to Cladribine tablet in a placebo-controlled study (CLARITY trial). The population was 18 to 65 years of age, and gender distribution was approximately 2:1 female to male. 91.2% in the Cladribine tablet 3.5 mg/kg group and 86.2% in the 5.25 mg/kg group completed all treatment courses (refer to CLINICAL TRIALS).

Table 3 shows all treatment emergent adverse events occurring at any time during the CLARITY trial with an incidence ≥ 5% in any treatment group.

Table 3: Treatment emergent adverse events occurring at any time during the CLARITY trial with an incidence ≥ 5% in any treatment group

System organ class Preferred term [1]	**Number of Patients (percent)**		
	Cladribine tablet 3.5 mg/kg [n = 430]	**Cladribine tablet 5.25 mg/kg** [n = 454]	**Placebo** [n = 435] [2]
Infections and infestations			
Nasopharyngitis	62 (14.4)	58 (12.8)	56 (12.9)
Upper respiratory tract infection	54 (12.6)	52 (11.5)	42 (9.7)
Urinary tract infection	23 (5.3)	33 (7.3)	39 (9.0)
Influenza	28 (6.5)	34 (7.5)	27 (6.2)
Gastrointestinal disorders			
Nausea	43 (10.0)	50 (11.0)	39 (9.0)
Diarrhoea	30 (7.0)	31 (6.8)	29 (6.7)
Nervous system disorders			
Headache	104 (24.2)	94 (20.7)	75 (17.2)
Blood and lymphatic system disorders			
Lymphopenia	93 (21.6)	143 (31.5)	8 (1.8)
Leucopenia	24 (5.6)	39 (8.6)	3 (0.7)
Musculoskeletal and connective tissue disorders			
Back pain	34 (7.9)	39 (8.6)	28 (6.4)

Table 3: Treatment emergent adverse events occurring at any time during the CLARITY trial with an incidence ≥ 5% in any treatment group			
System organ class Preferred term [1]	**Number of Patients (percent)**		
	Cladribine tablet 3.5 mg/kg [n = 430]	**Cladribine tablet 5.25 mg/kg** [n = 454]	**Placebo** [n = 435] [2]
Arthralgia	27 (6.3)	23 (5.1)	21 (4.8)
Pain in extremity	16 (3.7)	25 (5.5)	21 (4.8)
General disorders and administration site conditions			
Influenza like illness	34 (7.9)	27 (5.9)	31 (7.1)
Fatigue	20 (4.7)	27 (5.9)	26 (6.0)
Respiratory, thoracic and mediastinal disorders			
Pharyngolaryngeal pain	19 (4.4)	24 (5.3)	25 (5.7)
Psychiatric disorders			
Depression	18 (4.2)	25 (5.5)	13 (3.0)
Insomnia	25 (5.8)	14 (3.1)	17 (3.9)
Investigations			
Lymphocyte count decreased	13 (3.0)	26 (5.7)	0
Ear and labyrinth disorders			
Vertigo	14 (3.3)	23 (5.1)	11 (2.5)

[1] MedDRA dictionary

[2] two patients in the placebo group had actually received a small amount of cladribine

List of adverse reactions

Listed below are adverse reactions (i.e. causal association with the treatment is considered at least possible) derived from clinical studies with Cladribine tablet in MS, including those with lower incidence than 5%.

The following definitions apply to the frequency terminology:

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

Infections and infestations

Common: Oral herpes, dermatomal herpes zoster

Very rare: Tuberculosis.

Blood and lymphatic system disorders

Very common: Lymphopenia, which may be severe (grade 3 or 4)

Common: Decrease in neutrophil count

Skin and subcutaneous tissue disorders

Common: Rash (e.g. pustular, papular, macular, pruritic, erythematous rash), alopecia

Post-marketing data

Immune system disorders

Common: hypersensitivity including pruritus, urticaria, rash and rare cases of angio-oedema

Hepatobiliary disorders

Uncommon: Liver injury

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 with grade 3 lymphopenia 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 and strict criteria for initiating and continuing cladribine treatment must be followed (refer to 4.4 Special warnings and precautions for use and 4.2 Dose and method of administration).

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 Merck Cladribine.

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

There is limited experience with overdose of Cladribine tablet. Lymphopenia is known to be dose-dependent (refer to 4.4 Special warnings and precautions for use and 4.8 Undesirable effects).

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

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 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/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:CD8 ratio. Cladribine reduces CD19+ B cells and CD19+/CD56+ natural killer cells, which also recover faster than CD4+ T cells.

Clinical efficacy and safety

Efficacy and safety of Cladribine tablet tablets for oral use were evaluated in relapsing-remitting MS in the Cladribine Tablets Treating MS Orally (CLARITY) trial, a randomised, multicentre, double-blind, placebo-controlled clinical study in which 1326 patients were enrolled and randomly assigned to receive either placebo (n = 437), or a cumulative dose of Cladribine tablet of either 3.5 mg/kg (n = 433) or 5.25 mg/kg (n = 456) in 2 treatment courses over the 96 week (2-year) trial period.

Cladribine tablet was administered orally as 10 mg tablets, with the number of tablets taken daily based on the patient's body weight using 10 kg weight ranges. 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 (86.3%) and the Cladribine tablet 3.5 mg/kg (91.2%) and 5.25 mg/kg (86.2%) treatment groups completed both treatment courses through 52 weeks. A correspondingly high proportion of patients in the placebo and the Cladribine tablet 3.5 mg/kg and 5.25 mg/kg treatment groups (87.0%, 91.9%, and 89.0%, respectively) completed the full 96 weeks of the trial.

In the overall trial population, the median age was 39 years (range 18 to 65), and the female to male ratio was approximately 2:1. The median duration of MS prior to trial enrolment was 6.7 years, and the median baseline neurological disability based on Expanded Disability Status Scale (EDSS) score across all treatment groups was 3.0 (range 0 to 6.0). The mean number of T1 gadolinium-enhancing (Gd+) lesions, T1 hypointense lesions, and mean T2 lesion volumes were 0.93, 7.7, and 15,467 mm^3, respectively. Over two thirds of the trial patients were treatment-naive for MS disease-modifying medications.

Both Cladribine tablet treatment groups, 5.25 mg/kg and 3.5 mg/kg, were significantly superior to placebo in the treatment of relapsing-remitting MS. Clinical outcomes are shown in Table 4.

Table 4: Clinical Outcomes in the CLARITY Trial

Parameter	**Placebo**	**Cladribine tablet Cumulative Dose**	
		3.5 mg/kg	**5.25 mg/kg**
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 in annualised relapse rate (%) (95% CI)		57.6 * (46, 66)	54.5 * (46, 65)

Table 4: Clinical Outcomes in the CLARITY Trial			
Parameter	**Placebo**	**Cladribine tablet Cumulative Dose**	
		3.5 mg/kg	**5.25 mg/kg**
Proportion of patients relapse-free over 96 weeks	60.9%	79.7%	78.9%
Odds ratio (95% CI)		2.53 * (1.87, 3.43)	2.43 * (1.81, 3.27)
Time to first relapse (weeks) 15th percentile	20.1	58.3	58.0
Hazard ratio (95% CI)		0.44 * (0.34, 0.58)	0.46 * (0.36, 0.60)
Proportion of patients sustained disability-free over 96 weeks	79.4%	85.7%	84.9%
Odds ratio (95% CI)		1.55 ** (1.09, 2.22)	1.46 ** (1.03, 2.07)
Time to 3-month EDSS progression hazard ratio (95% CI)		0.67 ** (0.48, 0.93)	0.69 ** (0.49, 0.96)

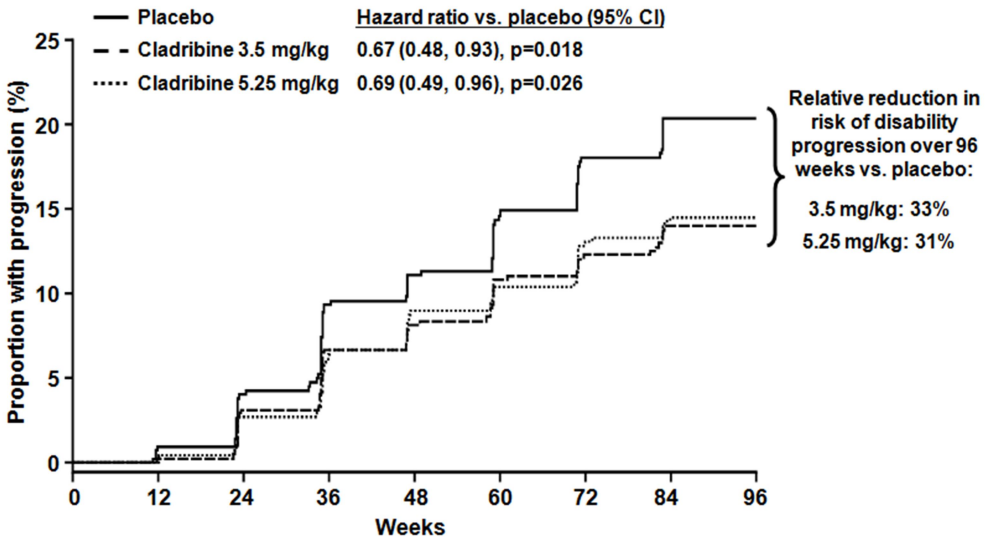
* $p < 0.001$ compared to placebo

** $p < 0.05$ compared to placebo

Time to sustained disability progression was defined as the time to worsening in EDSS score of ≥ 1 unit if baseline EDSS was 0.5 to 4.5, or ≥ 1.5 units if baseline EDSS was 0, or ≥ 0.5 unit if EDSS was ≥ 5, and persistent for at least 12 weeks. Treatment with Cladribine tablet 3.5 mg/kg and 5.25 mg/kg resulted in a prolongation in time to sustained disability progression of 12 weeks (10th percentile, both treatment groups) compared with placebo (Figure 1).

The 3.5 mg/kg and 5.25 mg/kg treatment groups had a 33% and a 31% relative reduction in risk of developing disability progression over the 96-week trial period, respectively, compared with the placebo group (hazard ratio = 0.67, 95% CI [0.48, 0.93], p = 0.018; hazard ratio 0.69, 95% CI [0.49, 0.96], p = 0.026, respectively). The proportion of patients progressing to sustained disability was 20.6% in the placebo group, 14.3% in the 3.5 mg/kg treatment group and 15.1% in the 5.25 mg/kg treatment group.

Figure 1: Proportion of Patients with Sustained Disability Progression*



* The hazard ratio, 95% CI and p-values were estimated using Cox proportional hazards model with fixed effects for treatment group and region.

In addition, both Cladribine tablet treatment groups were statistically significantly superior to placebo with regard to number and relative reduction of T1 Gd+ enhancing lesions, active T2 lesions and combined unique lesions as demonstrated on brain magnetic resonance imaging (MRI) over the entire 96 weeks of the trial. Patients in the Cladribine tablet 3.5 mg/kg and the 5.25 mg/kg treatment groups compared to the placebo treatment group had 86% and 88% relative reductions in the mean number of T1 GD+ lesions, 73% and 77% relative reductions in the mean number of active T2 lesions, and 74% and 78% relative reductions, in the mean number of combined unique lesions per patient per scan ($p < 0.001$ for both groups across all 3 MRI outcomes).

As shown in Table 1 above, a higher cumulative dose did not add any clinically meaningful benefit, but was 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).

Post hoc analysis showed a greater relative reduction in risk of relapse over 2 years for patients with highly active disease prior to receiving cladribine than in the overall patient population (68% reduction compared with 58% overall). The relative risk of 3-month disability progression over 2 years was reduced to a greater extent in patients with more active disease at baseline (72% reduction compared with 33% overall).

Subgroup analyses of region, gender, age and relapse history all showed positive treatment effects from both doses of Cladribine tablet with no large differences between subgroups.

Patients who had completed the CLARITY study could be enrolled in CLARITY Extension (EXT) study. 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.

Of these, 98 patients treated for 2 years in CLARITY with Cladribine tablet 3.5 mg/kg were switched to placebo for 2 years in CLARITY EXT. The magnitude of the effect in reducing the frequency of relapses and slowing disability progression in patients receiving the 3.5 mg/kg dose in years 1 and 2 was maintained during CLARITY EXT (in years 3 and 4). The annualised relapse rate was 0.15 and 72.4% of these patients did not experience 3-month confirmed disability progression during CLARITY EXT. Also, the group continued to exhibit low T1-Gd+ lesion activity.

In CLARITY EXT study, no additional efficacy was demonstrated when patients were given additional treatment courses of Cladribine tablet (n=186) in years 3 and 4.

5.2 Pharmacokinetic properties

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

Absorption

Following oral administration of Cladribine tablet tablets, cladribine is absorbed rapidly. Administration of 10 mg tablets resulted in a 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, absorption of cladribine 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 oral bioavailability of cladribine 10 mg was approximately 40%.

Distribution

The volume of distribution is large, indicating extensive tissue distribution and intracellular uptake. The mean volume of distribution of cladribine was estimated as 487 L (SD ± 180). The plasma protein binding is 20%, and independent of plasma concentration. Intracellular concentrations of phosphorylated cladribine were found to be several hundred-folds higher than corresponding plasma concentrations.

Cladribine is able to penetrate the blood brain barrier as shown by a cerebrospinal fluid/plasma concentration ratio of approximately 0.25.

Metabolism

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

In hepatic *in vitro* systems, minor metabolism of cladribine was observed (92% to 99% was unchanged cladribine). *In vitro* studies also showed negligible transporter-mediated uptake of cladribine into human hepatocytes.

After entering the cell, cladribine is phosphorylated to cladribine monophosphate (Cd-AMP) by deoxycytidine kinase (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´-nucleotidase.

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 $t_{1/2}$ of Cd-AMP was 15 h. Intracellular $t_{1/2}$ of Cd-ATP was 10 h.

Elimination

The renal and the non-renal routes of cladribine elimination are approximately equally important. Based on pooled population pharmacokinetic data from various studies, the median values for the two elimination routes 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 secretion of cladribine.

The non-renal part of the elimination of Cladribine tablet (approximately 50%) consists of fractional hepatic metabolism and presumably 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 pharmacokinetics of cladribine are best described by a three-compartment model where 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 tablets across a dose range from 3 mg to 20 mg, C_{max} and AUC increase in a linear dose-proportional fashion, suggesting that absorption is not affected by rate- or capacity-limited processes up to a 20 mg oral dose.

No accumulation of cladribine plasma concentrations have been observed after repeated dosing.

There is no indication that cladribine pharmacokinetic parameters might change in a time-dependent fashion after repeated administration.

Special populations

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

A population pharmacokinetic analysis did not show any effect of age (range 18 to 65 years) or gender on cladribine pharmacokinetics. The effect of age < 18 years and > 65 years on cladribine pharmacokinetics has not been studied.

The results of the clinical trials did not show any evidence of cardiotoxicity, however patients with significant cardiac pathology, such as angina, congestive heart failure or arrhythmias, were not eligible to be enrolled in the clinical trials.

Renal impairment

Renal and non-renal routes are equally important for the elimination of Cladribine tablet. Total clearance 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 importance of hepatic function for the elimination of cladribine is considered low.

5.3 Preclinical safety data

Carcinogenicity

While no treatment-related tumours were seen in a 26-week carcinogenicity study in transgenic mice by oral administration, an increased incidence of Harderian gland adenomas was seen in a 22-month carcinogenicity study in mice by subcutaneous administration. The clinical relevance of this is unclear as humans do not have this anatomical structure. However, based on its mode of action and positive findings in mammalian genotoxicity tests (*in vitro* and *in vivo*), a carcinogenic potential of cladribine cannot be excluded.

Genotoxicity

Cladribine was shown to be genotoxic, causing chromosomal damage in the bone marrow of mice *in vivo* and in CHO-WBL cells *in vitro*. These findings are expected since cladribine is known to cause inhibition of DNA synthesis by an imbalance of deoxynucleotide triphosphate pools, DNA strand breaks, inhibition of DNA repair, and depletion of intracellular nicotinamide adenine dinucleotide (NAD). Cladribine was not mutagenic *in vitro* (bacterial and mammalian cell mutation assays) and did not induce unscheduled DNA synthesis in primary rat hepatocyte cultures.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropylbetadex, sorbitol and magnesium stearate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Protect from moisture. Store below 30°C in the original container.

6.5 Nature and contents of container

Tablets 10 mg (uncoated, white, round, biconvex tablets engraved with 'C' on one side and '10' on the other) in an aluminium-aluminium blister, sealed in a cardboard wallet and fixed in a child-resistant carton: packs of 1, 4, 5, 6, 7 or 8 tablets*.
*Not all pack sizes may be marketed.

6.6 Special precautions for disposal

For disposal of any expired, damaged or unused, return to pharmacist.
Medicines should not be disposed of via wastewater or household waste.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Supplied in New Zealand by:
Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks, Auckland
For enquiries call: 0800 426 252

Supplied in Australia by:
Merck Healthcare Pty Ltd
Suite 1, Level 1, Building B
11 Talavera Road
Macquarie Park NSW 2113

9 DATE OF FIRST APPROVAL

1 August 2019

10 DATE OF REVISION OF THE TEXT

21 February 2022

SUMMARY TABLE OF CHANGES

Sections changed	Summary of new information
4.4, 4.5, 4.6, 4.8	Minor editorial changes
4.8	Additional information regarding liver injury as an adverse reaction