Clinical Pharmacokinetics (2019) 58:283–297
https://doi.org/10.1007/s40262-018-0695-9

REVIEW ARTICLE

The Clinical Pharmacology of Cladribine Tablets for the Treatment of Relapsing Multiple Sclerosis

Robert Hermann[1] · Mats O. Karlsson[2] · Ana M. Novakovic[3] · Nadia Terranova[4] · Markus Fluck[3] · Alain Munafo[4]

Published online: 10 July 2018

Abstract

Cladribine Tablets (MAVENCLAD®) are used to treat relapsing multiple sclerosis (MS). The recommended dose is 3.5 mg/kg, consisting of 2 annual courses, each comprising 2 treatment weeks 1 month apart. We reviewed the clinical pharmacology of Cladribine Tablets in patients with MS, including pharmacokinetic and pharmacometric data. Cladribine Tablets are rapidly absorbed, with a median time to reach maximum concentration (T_{max}) of 0.5 h (range 0.5–1.5 h) in fasted patients. When administered with food, absorption is delayed (median T_{max} 1.5 h, range 1–3 h), and maximum concentration (C_{max}) is reduced by 29% (based on geometric mean). Area under the concentration–time curve (AUC) is essentially unchanged. Oral bioavailability of cladribine is approximately 40%, pharmacokinetics are linear and time-independent, and volume of distribution is 480–490 L. Plasma protein binding is 20%, independent of cladribine plasma concentration. Cladribine is rapidly distributed to lymphocytes and retained (either as parent drug or its phosphorylated metabolites), resulting in approximately 30- to 40-fold intracellular accumulation versus extracellular concentrations as early as 1 h after cladribine exposure. Cytochrome P450-mediated biotransformation of cladribine is of minor importance. Cladribine elimination is equally dependent on renal and non-renal routes. In vitro studies indicate that cladribine efflux is minimally P-glycoprotein (P-gp)-related, and clinically relevant interactions with P-gp inhibitors are not expected. Cladribine distribution across membranes is primarily facilitated by equilibrative nucleoside transporter (ENT) 1, concentrative nucleoside transporter (CNT) 3 and breast cancer resistance protein (BCRP), and there is no evidence of any cladribine-related effect on heart rate, atrioventricular conduction or cardiac repolarisation (QTc interval prolongation). Cladribine Tablets are associated with targeted lymphocyte reduction and durable efficacy, with the exposure–effect relationship showing the recommended dose is appropriate in reducing relapse risk.

Key Points

This review discusses the clinical pharmacology of Cladribine Tablets in patients with relapsing multiple sclerosis, presenting pharmacokinetic, pharmacodynamic and pharmacometric data.

Cladribine Tablets are associated with a selective reduction in lymphocyte counts and durable efficacy relative to the fast disposition in plasma, and short-term treatment posology in each of the 2 treatment years.

The recommended cumulative dose of Cladribine Tablets 3.5 mg/kg over 2 years is shown to be appropriate in reducing relapse risk.

✉ Robert Hermann
robert.hermann@cr-appliance.com

[1] Clinical Research Appliance (Cr Appliance), Heinrich-Vingerhut-Weg 3, 63571 Gelnhausen, Germany

[2] Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

[3] Merck KGaA, Darmstadt, Germany

[4] Merck Institute for Pharmacometrics, Merck Serono S.A., Switzerland, an Affiliate of Merck KGaA, Darmstadt, Germany

1 Introduction

Multiple sclerosis (MS) is a neurodegenerative disease, where a patient's immune system attacks their central nervous system, resulting in demyelination, axonal damage and progressive disability [1, 2]. Cladribine Tablets (MAVENCLAD®; Merck Serono Europe Ltd), an oral formulation of cladribine, were shown to have significant efficacy for the treatment of relapsing MS in placebo-controlled, phase III trials [3–5]. A cumulative dose of 3.5 mg/kg body weight (consisting of 2 annual courses that are each comprised of 2 treatment weeks; 1 at the start of the first month and 1 at the start of second month of each year) has been approved for the treatment of adults with certain types of relapsing MS [6–8]. The short-term treatment posology of Cladribine Tablets has the potential to facilitate patient adherence [4], which is an ongoing challenge for the long-term treatment of MS [9].

Cladribine is a nucleoside analogue of deoxyadenosine. The cladribine prodrug is phosphorylated intracellularly to its active product, 2-chlorodeoxyadenosine triphosphate (Cd-ATP), by deoxycytidine kinase. This deoxynucleotide product is degraded in most cells, by 5′-nucleotidase. Cells such as lymphocytes that contain a high deoxycytidine kinase activity but low 5′-nucleotidase activity, i.e. a high deoxycytidine kinase to 5′-nucleotidase activity ratio, accumulate deoxynucleotides to toxic concentrations, resulting in lymphocyte cell death. By this mechanism, Cladribine Tablets exert a selective mode of action on B and T lymphocytes [10, 11]. Variations in the expression levels of deoxycytidine kinase and 5′-nucleotidase between immune cell subtypes 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 [12, 13]. Cladribine Tablets have been described as a selective immune reconstitution therapy due to their selective effect on the adaptive versus innate immune system, together with the short and intermittent nature of the treatment courses [14, 15]. The current theory is that by inducing lymphopenia, Cladribine Tablets reset the immune system [15].

Cladribine was first established as a parenteral formulation for the treatment of B- and T cell lymphoid malignancies, including hairy cell leukaemia and chronic lymphocytic leukaemia [16, 17]. The clinical pharmacokinetics (PK) of parenteral cladribine in patients with malignancies were previously reported by Liliemark in 1997 [18], reflecting the state of knowledge at that time. Due to the recent approval of Cladribine Tablets, a decision that was based on a substantial amount of new study data, an up-to-date review of the clinical pharmacology of cladribine is warranted [3, 19, 20]. Here, we review the clinical PK and outcomes of pharmacometric analyses (PK and primary pharmacodynamics [PD]) of the oral tablet formulation of cladribine in patients with MS in order to provide a comprehensive and timely summary of the available data. This report represents a narrative review of data from publications, congress materials, label information, and unpublished data on file.

2 Pharmacokinetics (PK)

2.1 Overview of Studies

The PK of Cladribine Tablets has been investigated in 5 phase I studies in patients with MS, plus a subpopulation of the phase III CLARITY clinical trial. A summary of the phase I studies is presented in Table 1. In addition, data from 3 of the PK studies (studies 25803, 26127 and 26486) plus the PK subpopulation from the CLARITY clinical trial (see footnote in Table 2) were recently combined in a population PK analysis [19]. The population PK analysis was performed

Table 1 Phase I pharmacokinetics studies of Cladribine Tablets

Study number	Study description	Number of patients	Cladribine dose and administration method	Included in population pharmacokinetic analysis?	References
IXR-102-09-186	Absolute bioavailability study	26	3 mg intravenous/3 and 10 mg single oral tablets	No	[21]
25803	Bioavailability and metabolite study	16	3 mg intravenous/10 mg single oral tablet	Yes	[19]
26127	Food interaction study (high-fat breakfast)	16	10 mg single oral tablet	Yes	[19]
26486	Drug interaction study (interferon-β1a)	16	1.75 mg/kg cumulative dose of oral tablets over 8 weeks	Yes	[19]
27967	Study to assess interactions with pantoprazole	18	10 mg single oral tablet	No	[19]

Table 2 Phase III clinical trials of Cladribine Tablets

Trial name	Study description	Patients and treatment arms[a]	ClinicalTrials.gov identifier	References
A safety and efficacy study of oral cladribine in subjects with relapsing–remitting multiple sclerosis (CLARITY)	Randomised, double-blind, 3-arm, placebo-controlled, multicentre study to evaluate the safety and efficacy of oral cladribine in subjects with relapsing–remitting multiple sclerosis	CT 3.5, $n=433$[b] CT 5.25, $n=456$[b] PBO, $n=437$	NCT00213135	[3]
CLARITY extension	Double-blind, placebo-controlled, multicentre, parallel group, extension trial to evaluate the safety and tolerability of oral cladribine in subjects with relapsing–remitting multiple sclerosis who have completed the CLARITY trial	CT 3.5 → PBO, $n=98$ CT 5.25 → PBO, $n=92$ CT 3.5 → CT 3.5, $n=186$ CT 5.25 → CT 3.5, $n=186$ PBO → CT 3.5, $n=244$	NCT00641537	[4]
Oral cladribine in early multiple sclerosis (ORACLE-MS)	Randomised, double-blind, clinical trial to assess the safety and efficacy of 2 doses of Cladribine Tablets versus placebo in patients who had a first clinical demyelinating event (clinically isolated syndrome)	CT 3.5, $n=206$ CT 5.25, $n=204$ PBO, $n=206$	NCT00725985	[5]

CT 3.5 Cladribine Tablets 3.5 mg/kg cumulative dose over 2 years, *CT 5.25* Cladribine Tablets 5.25 mg/kg cumulative dose over 2 years, *PBO* placebo

[a]Treatment arms in the CLARITY Extension study are shown as the CLARITY treatment on the left side of the arrow and the CLARITY Extension treatment on the right side of the arrow

[b]A subpopulation of 125 patients from the CT 3.5 and CT 5.25 treatment groups in the CLARITY study provided samples for pharmacokinetics analyses, including the population pharmacokinetic analysis by Savic et al. [19]

to characterise the concentration–time course of cladribine, to estimate interindividual variability in PK, and to identify covariates that explain such variability.

2.2 Absorption

Cladribine is rapidly absorbed after tablet administration (Fig. 1); oral administration of a single 10 mg tablet in a fasted state is associated with a median time to reach maximum concentration (T_{max}) of approximately 0.5 h (range 0.5–1.5 h) [21]. The mean maximum concentration (C_{max}) is in the range of 22–29 ng/mL, with the corresponding mean area under the concentration–time curve (AUC) in the range of 80–101 ng·h/mL (arithmetic means from various studies) [22]. Cladribine can be considered a Biopharmaceutics Classification System (BCS) class III compound (low permeability, high solubility) [20]. The oral bioavailability of Cladribine Tablets when administered in the fasted state is approximately 40% [22], possibly limited by breast cancer resistance protein (BCRP)-mediated intestinal efflux. In the phase III studies, patients were instructed to take their tablets after an overnight fast on an empty stomach, and, once administered, to wait at least 1 h before eating. If a dose was to be administered in the afternoon, or if a subject had mistakenly eaten before dosing, subjects were to wait at least 4 h after eating their last meal before dosing. In a phase I study, it was shown that taking a single 10 mg Cladribine Tablet after a high-fat breakfast results in a delay of the median T_{max} from 0.5 h in the fasted state to 1.5 h (range 1–3 h) in the fed state [22]. This is associated with a 29% reduction in the maximum exposure of cladribine (geometric mean C_{max}) compared with administration after an overnight fast, while the total exposure (estimated by noncompartment analysis) is minimally affected (geometric mean AUC from time zero to infinity (AUC_{∞}) was 72.8 ng·h/mL for the fed state versus 75.7 ng·h/mL for the fasted state). Cladribine Tablets can therefore be administered without regard to food [22]. In the population PK analysis, absorption in the fasted state was described by a first-order process, and a transit-compartment model described the absorption delay in the data from the fed state. The fed/fasted status of phase III subjects was classified as 'unknown' for modelling purposes. For phase III subjects, the rate of absorption and bioavailability estimates were the same or very similar to the values for fed subjects, and absorption delay was more similar to the estimated value for fasted subjects. Oral bioavailability of Cladribine Tablets was estimated to be 45.6%, and coadministration with a high-fat meal resulted in a modest change in bioavailability to 40.5%, and a modest delay in absorption (Fig. 2). This was not expected to have a clinically meaningful impact [19]. Taken together, the noncompartmental and population PK

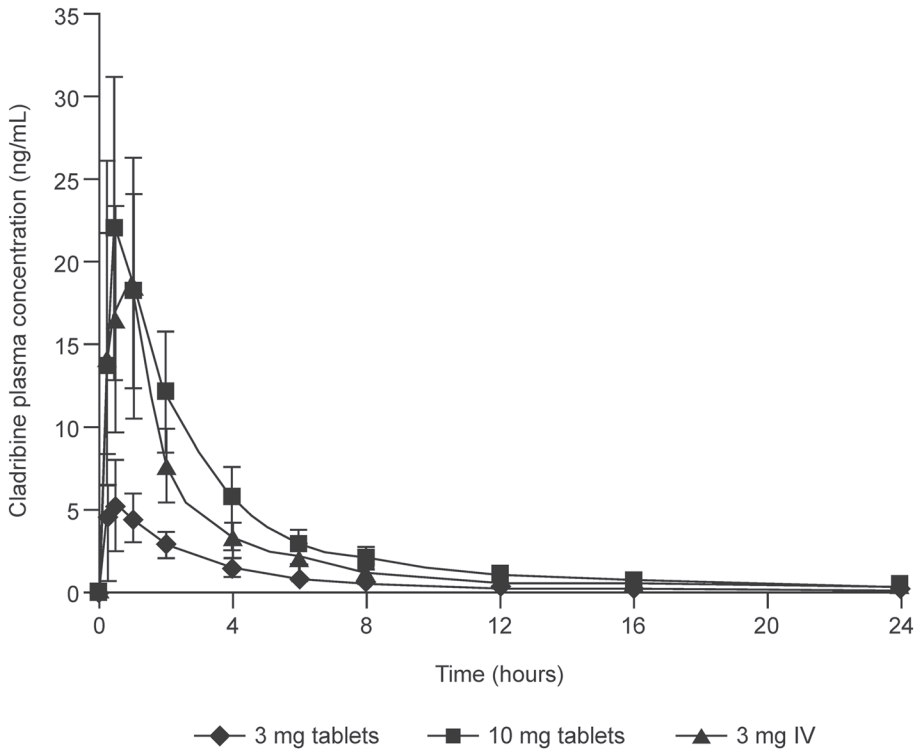

Fig. 1 Mean (standard deviation) plasma cladribine concentration by treatment. *IV* intravenous. Adapted from Munafo et al. [21]

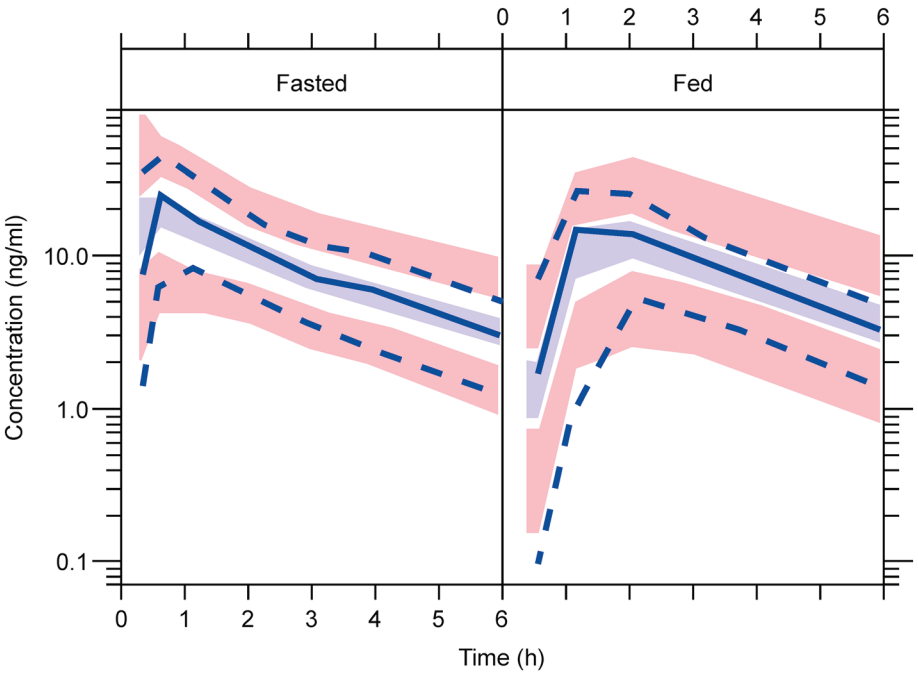

Fig. 2 Population pharmacokinetic visual predictive checks for plasma cladribine concentrations in fasted and fed conditions. Light blue shaded area indicates simulated median with uncertainty; pink shaded area indicates simulated 5th and 95th percentiles with uncertainty; solid blue line indicates observed median; dashed blue line indicates observed 5th and 95th percentiles. Adapted from Savic et al. [19]. © The Authors 2017

analyses of cladribine bioavailability, rate of absorption, and food effects yielded consistent results.

2.3 Distribution

The volume of distribution of cladribine is large, in the range of 480–490 L, which indicates extensive tissue distribution and intracellular uptake [19, 22]. Various transporter proteins facilitate the distribution of cladribine across biological membranes, including equilibrative nucleoside transporter (ENT) 1, concentrative nucleoside transporter (CNT) 3 and BCRP. Cladribine is most likely transported into lymphocytes by ENT1 and CNT3 [23, 24]. The ENT1 transporter protein is also thought to be an important contributor to

the active efflux of cladribine from white blood cells [25]. The oral bioavailability of cladribine may be limited by the efflux transporter BCRP, which has an affinity with cladribine (BCRP overexpression has been shown to strongly reduce the rate of 2-CdA accumulation in human osteosarcoma cells) [26] and is expressed at high levels in the small intestine [27]. The contribution of P-glycoprotein (P-gp; ABCB1) to cladribine efflux is probably not important for the overall bioavailability of Cladribine Tablets, based on results of studies in MDCKII-MDR1 cells that show P-gp is not an efficient transporter of cladribine [22, 28]. Clinically relevant interactions with inhibitors of P-gp are therefore not expected.

Results of an uptake study of ^{14}C-labelled cladribine into cryopreserved human hepatocytes suggest that transporter-mediated uptake of cladribine into human hepatocytes is negligible (data on file). Cladribine and/or its phosphorylated metabolites are substantially accumulated and retained in human lymphocytes. As shown in vitro, cladribine is rapidly distributed to, and retained in (either as parent drug or its phosphorylated metabolites), human lymphocytes, resulting in approximately 30- to 40-fold intracellular accumulation compared with extracellular concentrations, as early as 1 h after cladribine exposure (data on file). Cladribine has the potential to penetrate the blood–brain barrier [18]. A small study in another indication has shown a cerebrospinal fluid/plasma concentration ratio of approximately 0.25 [29]. In spiked human plasma, the plasma protein binding of cladribine was 20%, and independent of plasma cladribine concentration (data on file).

2.4 Metabolism

Cladribine metabolism was investigated in patients with MS following the administration of a single 10 mg tablet and a single 3 mg intravenous dose (study 25803) (Table 1). 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, i.e. amounting to $\leq$ 3% of the AUC of parent compound in plasma after oral administration. Only traces of other metabolites could be found in plasma and urine [30]. In hepatic in vitro systems, cladribine was only metabolised to a very low extent, with at least 90% of radiolabelled cladribine remaining unchanged (data on file).

Cladribine is not a relevant substrate to cytochrome P450 (CYP) enzymes, based on reaction phenotyping studies where cladribine was incubated with microsomes prepared from human recombinant lymphoblastoid cells that were genetically engineered to express specific human CYP enzymes that may be responsible for the metabolism of cladribine in vitro: CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 (data on file).

After entering the target cells, 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 chlorodeoxyadenosine diphosphate (Cd-ADP), and Cd-ADP is in turn phosphorylated by 5′-nucleotidase to Cd-ATP [10, 11]. In a study of the intracellular PK of Cd-AMP and Cd-ATP in another indication, the levels of Cd-ATP were approximately half that of the Cd-AMP levels. The intracellular half-life of Cd-AMP was 15 h and the intracellular half-life of Cd-ATP was 10 h [31].

2.5 Elimination

The population PK analysis showed that renal and non-renal routes of cladribine elimination are of approximately equal importance; the median values were estimated to be 22.2 L/h for renal clearance and 23.4 L/h for non-renal clearance. Renal clearance correlated with creatinine clearance (CL_{CR}), and CL_{CR} was therefore used to predict renal cladribine clearance in patients with renal impairment using the population PK model, with the assumption that changes in CL_{CR} only affect the renal component of total cladribine clearance. Intersubject variability for non-renal clearance was estimated to be 7.6%. The nonrenal proportion of cladribine clearance (approximately 50%) comprises negligible hepatic metabolism with extensive intracellular distribution and trapping of Cd-ATP within lymphocytes, and the subsequent elimination of intracellular Cd-ATP according to lymphocyte elimination pathways and lifecycle [22].

Renal clearance appears to exceed glomerular filtration rate, indicating net tubular excretion in addition to glomerular filtration [19]. As cladribine was shown not to be a substrate of the kidney-specific basolateral transporters OCT2, OAT1, and OAT3, nor of the kidney-specific apical transporter OAT4 (data on file), only BCRP [26, 28], ENT1/2 and CNT2/3 [32] remain as conceivable candidate transporters for active tubular secretion of cladribine. Basolateral-located ENT1 is the most likely candidate to facilitate basolateral uptake of cladribine as none of the other basolateral candidates tested actually facilitated cladribine uptake. In the apical membrane of renal tubular cells, of the 3 transporters implicated in renal transport of cladribine, only BCRP has been unambiguously shown to transport cladribine efficiently in multiple expression systems. P-gp-mediated transport does not seem to be efficient, and, for MRP4, transport was not shown in either of the test systems studied (HEK293-MRP4, MDCKII-MRP4; data on file). Based on these findings, the apical efflux is likely driven by BCRP, with some contribution of ENT1.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.