

Cladribine

Fact Sheet



Information

Education

Research

Support

Cladribine

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Contents

Section	Page
1. Introduction	1
2. How cladribine works	2
3. Research	2
4. Side effects and contraindications	3
5. Licensing	4
6. Further information	4
7. References	4

1. Introduction

All of the currently licensed disease modifying drug treatments for MS are given by injection or intravenous infusion (a drip into a vein of the arm). There are several drugs in development for the treatment of multiple sclerosis amongst which are a number of oral drugs including cladribine. This factsheet aims to explain how cladribine is thought to work and what has been shown in clinical trials of cladribine to date.

Cladribine is a form of chemotherapy that is used in the treatment of leukaemia. An oral version of the drug (brand name Movectro) with a different dosing pattern is being investigated as a potential treatment for relapsing remitting MS.

Cladribine has been studied against placebo for its effectiveness as a treatment for relapsing remitting MS. It is also being studied for its effects

when used in combination with beta interferon (as an add-on therapy) in people who continue to have relapses whilst receiving beta interferon.

2. How cladribine works

The autoimmune attack that is seen in MS results in the destruction of myelin, the substance covering and protecting nerves in the central nervous system. As with other chemotherapy drugs used in the treatment of MS, cladribine is used to kill off certain immune cells (lymphocytes) that prompt the autoimmune destruction of myelin. By reducing the number of destructive immune cells in circulation, it is thought it may slow down or stop this autoimmune attack.

3. Research

- CLARITY: CLAdRIbine Tablets Treating MS Orally

This two-year phase III trial studied the effects of oral cladribine in people with relapsing remitting MS. 1,326 people were allocated to one of three different treatment groups: low dose cladribine, high dose cladribine, or placebo.

The low dose cladribine treatment group received two courses for the first and second year; the high dose cladribine treatment group received four courses for the first year and two courses for the second year. Each course consisted of a once daily tablet for four to five consecutive days.

A 58% relative reduction in yearly relapse rate was seen in the low dose treatment group and a 55% reduction in the high dose treatment group. A reduction in the number of MS lesions as seen on MRI was also observed in the cladribine treatment groups and there was a higher proportion of people who remained relapse free over the study period.¹

- The CLARITY extension study

A two year extension of the CLARITY study is investigating the long-term effects of cladribine tablets for up to four years. People in the placebo arm of the original CLARITY study will receive cladribine tablets while people in the two cladribine treatment groups will be allocated to receive either cladribine or placebo.²

There are two further studies of oral cladribine currently underway:

- The ORACLE MS (**ORAI CL**adribine in **Early MS**) study.

A Phase III placebo-controlled trial is recruiting to investigate the effects of cladribine in people who have had a first event (first attack) suggestive of MS. The study will compare the progress of people who receive cladribine alongside people who receive a placebo to determine whether cladribine can delay conversion to definite MS (signified by a second attack or relapse). Two different doses of cladribine are being used in this study to determine any dose-dependent effects. This trial expects to complete in 2012.³

- The ONWARD (**O**ral Cladribine Added **ON** To Rebif New Formulation in Patients **With Active Relapsing Disease**) study

This Phase II placebo-controlled trial is studying the effects of cladribine as an add-on therapy in people with relapsing forms of MS who continue to show signs of active disease whilst on interferon beta treatment. Two different doses of cladribine are also being used in this study. This trial is fully recruited and expects to complete in 2013.⁴

4. Side effects and contraindications

Although the trials so far have shown cladribine to be well tolerated, lymphopenia - an abnormally low level of lymphocytes (white blood cells that fight off disease) occurred more frequently in the cladribine treatment groups. With the exception of lymphopenia, headaches and nasopharyngitis (inflammation of the nasal passages and upper part of the throat) were the most frequently reported adverse events in the three treatment groups. An increased number of people with cancer have also been observed in clinical trials of cladribine which could point to an increased risk of cancer over time and with increasing doses of the drug.

5. Licensing

In September 2010, the European Medicines Agency (EMA) rejected the licence application for cladribine.

The regulators found that the benefits of the drug did not outweigh the risks. They raised concerns about four cases of cancer observed during clinical testing and about the drug's effect on the immune system.

The manufacturer, Merck KGaA, appealed, but in January 2011 the EMA confirmed its original decision. The US Food and Drug Administration (FDA) had also asked for further trials before granting a licence.

In June 2011, Merck announced that they were discontinuing their applications for licences for cladribine saying, "We believe that data from ongoing clinical trials are very unlikely to address the FDA's requirements." Cladribine was also withdrawn in Australia and Russia where licences had already been granted.

6. Further information

ClinalTrials.gov

For further information about current and completed clinical trials of cladribine tablets visit www.clinicaltrials.gov. ClinicalTrials.gov is a registry clinical trials conducted around the world. The site provides information about a trial's purpose, who may participate, and trial locations. This information should be used in conjunction with advice from health care professionals.

7. References

1. Giovannoni G, Comi G, Cook S, et al.
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4. Current Controlled Trials website.
Phase II cladribine add-on to interferon-beta (IFN- β) therapy in MS subjects with active disease.
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^ Note - Drug trials

Phase I studies primarily assess the safety of a drug or procedure. They usually involve a small number of healthy volunteers (10-100) all of whom are given the same treatment.

Once a medical intervention has been proven safe, phase II trials test its effectiveness and whether it has the potential to be of benefit. These trials are larger, typically involving 100-300 people with the condition for which the intervention has been developed - in this case MS.

If the phase II study shows the treatment to be beneficial, phase III studies are conducted to gain a definitive understanding of the effectiveness, benefits and potential side effects in a large group of people (300-3,000) with the condition to be treated. Interventions have to successfully complete a phase III trial before they can be considered for a licence by regulatory authorities.