Information Sheet

MSIreland
THE MULTIPLE SCLEROSIS SOCIETY OF IRELAND

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Mavenclad (Cladribine)

- **What is Mavenclad?**

  Mavenclad is a disease modifying drug for adults with highly active relapsing MS. It is a short course oral therapy that you take as a tablet in two treatment courses, twelve months apart. Following completion of the 2 treatment courses, no further cladribine treatment is required in years 3 and 4

- **How does Mavenclad work?**

  Mavenclad works by temporarily reducing the numbers of certain types of white blood cell (T and B lymphocytes). These are thought to be involved in the abnormal immune response which attacks the myelin coating of nerve cells that is believed to cause the damage associated with MS.

  After each treatment course of Mavenclad, patients' white blood cells will reduce and this is followed by a period of recovery. Patients' white blood cells must reach a certain level prior to retreatment in year 2. It is expected that most patients' white blood cells return to normal or almost normal within 9 months after completing year 2 treatment

- **Who should take Mavenclad?**

  Mavenclad can be prescribed for patients with Highly active Relapsing Multiple Sclerosis, as defined by clinical and Imaging features and can only be prescribed by a physician experienced in the treatment of MS

  Contraindications

  It is important that you tell your MS team if you have any health problems or are taking other medicines.

  Mavenclad must not be used if you have:
  Hypersensitivity (allergy) to the active drug or any other ingredients in the tablet
  If you have HIV, or infection with tuberculosis or hepatitis
  Active cancer
  If you are pregnant or breastfeeding

If you have moderate or severe Kidney problems (discuss with your doctor)
If you are already taking medication that affects your immune system, or if you have any other condition that may affect your immune system

Contraception and pregnancy

Mavenclad must not be used in pregnant women or by men and women while they are trying to conceive. In men, it could affect the development and quality of your sperm during treatment and for up to six months after treatment, and in women it could seriously harm your developing baby.

Contraception:

Both men and women should use effective contraception during treatment and for six months after taking Mavenclad to prevent pregnancy. Male patients must take precautions to prevent pregnancy of their female partner during cladribine treatment and for at least 6 months after the last dose.

If you are a woman using hormonal contraception (OCP, IUD, Patch, injection), you will need to use an additional barrier method of contraception during treatment and for 4 weeks after your last dose in each treatment year. This is because it is currently unknown whether Mavenclad may reduce the effectiveness of systemically-acting hormonal contraceptives. If you become pregnant while on treatment with Mavenclad, you should discontinue treatment and contact your neurologist or nurse as soon as possible.

Male patients must take precautions to prevent pregnancy of their female partner during cladribine treatment and for at least 6 months after the last dose. If your partner becomes pregnant, you should inform your neurologist or nurse as soon as possible.

Consult your HCP for advice on suitable contraception methods to prevent pregnancy during treatment with Mavenclad.

Female patients can start to try to conceive six months after completing the second course of treatment in year 2, to allow completion of the full treatment course of Mavenclad before getting pregnant. Male patients can try for a family six months after the last dose in both year 1 and year 2.

- **How is Mavenclad administered?**
  You take Mavenclad as a tablet in two treatment courses, twelve months apart:

- in the first course you take Mavenclad tablets for four or five consecutive days in the first month, and four or five consecutive days in the second month
- the second course is taken 12 months later; again, you take Mavenclad tablets for four or five consecutive days in the first month and four or five consecutive days in the second month.

The actual number of tablets you will take will depend on your weight.

Following completion of the two treatment courses, no further treatment is required in years 3 and 4. When Mavenclad was tested in clinical trials, No significant difference in outcomes were observed between patients who received Mavenclad treatment for four years continuously and those who took Mavenclad in years 1 and 2 and a placebo tablet in years 3 and 4.

- **What are the side-effects from taking Mavenclad?**
  The most common side effect is a reduction in the number of white blood cells called lymphocytes (lymphopenia), which is very common (may affect more than 1 in 10 people) and may be severe. Lymphopenia may increase the risk of getting an infection.

  Other common side effects - may affect between 1 in 100 people up to 1 in 10 people:
  - cold sore (oral herpes), shingles (varicella zoster)
  - rash
  - hair loss
  - reduction in the number of certain white blood cells (neutrophils)

A full list of side effects is included in the manufacturer's Patient Information Leaflet (link is external but data attached in email).

Assessment before treatment

Mavenclad can temporarily reduce the body's immune defence and may increase the likelihood of infections. This means that before starting treatment you will need to have tests to exclude any infections, in particular, tuberculosis, HIV and hepatitis. You will also need to have a test to check your body's immunity against varicella zoster (chickenpox/shingles) virus and if you don't have sufficient defence, you may need a vaccination to protect you.

You will also need to have a recent Magnetic Resonance Imaging scan (an MRI), this will need to be carried out within the 3 months prior to starting Mavenclad.

Assessment during treatment

When you have been prescribed Mavenclad, you must undergo scheduled blood tests before and after treatment in both years so that your healthcare team can monitor the level of your white blood cells.

These blood tests are scheduled at two intervals (2 and 6 months after treatment) in both years. Some patients may need to have additional monitoring if their white blood cells levels are slower to recover than others, which can then lead to a delay in starting their year 2 treatment as the white blood cells need to return to a required level prior to receiving the second year of treatment. If you do develop a very low white blood cell count after taking Mavenclad, your doctor may recommend that you take an anti-viral medication to prevent cold sores or shingles until your white blood cells increase again.

Are there any serious side effects from taking Mavenclad?

The most important side effect from taking MAVENCLAD is a reduction in the number of white blood cells called lymphocytes (**lymphopenia**), which is very common (may affect more than 1 in 10 people) and may be severe. Lymphopenia may increase the risk of getting infections or severe infections. An infection commonly seen with MAVENCLAD is **shingles (varicella zoster)**

A very rare side effect, (which may affect up to 1 in 10,000 people) is tuberculosis infection. You will need to have a test to exclude this infection prior to initiation of treatment of Mavenclad in both year 1 and 2.

If you have previously had cancer talk to your doctor before starting treatment with Mavenclad. This is because single events of cancer have been seen in those taking Mavenclad. The clinical trials of Mavenclad showed more cases of cancer in those taking Mavenclad compared to those taking placebo. However, further analysis of the trial data and comparison with data from a reference non-MS population showed that the type and frequency of cancers were the same as would be expected in people not on treatment. After taking Mavenclad you should continue to undergo standard cancer screening and your doctor can advise you about cancer screening programs appropriate for you. If you currently have an active cancer, you must not take Mavenclad.

Mavenclad should not be used by men or women while they are trying for a family, or in pregnant women. In men it could affect the development and quality of your sperm for up to six months after treatment, and in women it could seriously harm your developing baby. Women should use contraception for 6 months after taking the last dose in each treatment year. They can start to try to conceive six months after completing the second course of treatment in year 2, to allow completion of the full treatment course of Mavenclad before getting pregnant. Men can try for a family six months after the last dose in both year 1 and year 2.

Progressive multifocal leukoencephalopathy (PML)

If you believe your MS is getting worse or if you notice any new symptoms, for example changes in mood or behaviour, memory lapses, speech and communication difficulties, talk to your doctor as soon as possible. These may be the symptoms of a rare brain disorder, caused by an infection, and called progressive multifocal leukoencephalopathy (PML). PML is a serious condition that may lead to severe disability or death.

PML has not been observed in patients treated with MAVENCLAD but as a precaution, the MRI that you will have had before starting treatment along with your scheduled MRI monitoring help your team to monitor and screen for this infection.

What are the findings from the Mavenclad clinical trials?
Option 1

Mavenclad was studied in a large clinical trial, called CLARITY, in patients with the relapsing-remitting form of MS. The trial was designed to measure how well Mavenclad works (its efficacy) and to evaluate its safety, compared to placebo (a dummy treatment).

Compared to placebo, the patients taking Mavenclad had fewer relapses (58% reduction in the frequency)[1]. At the end of the 2 years, nearly 8 out of 10 patients taking Mavenclad had not had a

relapse, compared with 6 out of 10 taking placebo.[5] Patients taking Mavenclad were almost half as likely to have their disability get worse than those taking placebo. [1,2]

The results were greater for patients who had highly active MS; the reduction in the frequency of relapses was 67%[2,3] and they were 82%[1,2] less likely to have disability progression with Mavenclad compared to placebo. Mavenclad was therefore granted a licence for use in patients with highly active relapsing MS.[1]

Patients who completed the CLARITY study could be enrolled in a follow-up study for another 2 years (CLARITY EXTENSION). In this study, the effect of Mavenclad in reducing the frequency of relapses and slowing disability progression over the first 2 years was maintained in the majority of patients in years 3 and 4, but there seemed to be no additional benefit from giving more than 2 courses of Mavenclad treatment.[4]

Patients taking Mavenclad in the CLARITY trial were more likely to experience a reduction in their white blood cells (21.6% compared with 1.8% on placebo). This can increase the risk of getting infections, and more patients taking Mavenclad in the CLARITY trial developed shingles (8 patients on the standard dose and 12 patients on a higher dose of Mavenclad vs no patients on placebo).[5]

Option 2 : More detailed

Mavenclad was studied in a 2-year, phase 3 clinical trial (CLARITY) in patients with relapsing-remitting MS to measure how well it works (efficacy) and evaluate its safety, compared to placebo.

Compared to placebo, there was a reduction in relapse rate of 58% for Mavenclad patients (rate of relapses per year for Mavenclad was 0.14 and for placebo was 0.33)[1]. At the end of the 2 years, nearly 8 out of 10 patients taking Mavenclad had not had a relapse, compared with 6 out of 10 taking the placebo[5]. Patients taking Mavenclad were also 47%[1,2] less likely to have disability progression than people taking placebo.

For patients with high disease activity* there was a reduction in relapse rate of 67%[2,3] and they were 82%[1,2] less likely to have disability progression with Mavenclad compared to placebo. Mavenclad was therefore granted a licence for use in patients with highly active relapsing MS.[1]

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*High Disease Activity defined as patients with 2 or more relapses in the year before study entry, regardless of treatment status, or patients with 1 or more relapse in the year before study entry while on therapy with other DMDs and 1 or more T1Gd+ or 9 or more T2 lesions. [HAD-DAT][3]

1. Mavenclad Summary of Product Characteristics, January 2020.
2. Vermersch P. *et al*., 2018. Sustained efficacy in relapsing remitting multiple sclerosis following switch to placebo treatment from cladribine tablets in patients with high disease activity at baseline. Abstract A-0950-0028-00886. Poster presented at ECTRIMS, 10-12 October 2018, Berlin, Germany
3. Giovannoni G. *et al*., 2019. Efficacy of cladribine tablets in high disease activity subgroups of patient with relapsing multiple sclerosis: a post hoc analysis of the CLARITY study. *Multiple Sclerosis J* 2019; 25(6): 819-27.
4. Giovannoni G, Soelberg Sorensen P, Cook S, et al. Safety and efficacy of cladribine tablets in patients with relapsing-remitting multiple sclerosis: results from the randomized extension trial of the CLARITY study. Mult Scler. 2018;24:1594-604.
5. Giovanonni G *et al*., 2010. NEJM A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis. *N Engl J Med* ;362:416-26.
6. Cook s et al., 2019. Safety of cladribine tablets in the treatment of patients with multiple sclerosis: An integrated analysis. *Multiple Sclerosis And Related Disorders* 2019;29:157-167.

How does Mavenclad compare to current therapies? Mavenclad has not been directly compared with other MS therapies in clinical trials.

Is Mavenclad covered on a reimbursement scheme?

Yes, Mavenclad is reimbursed in Ireland for the treatment of adult patients with highly active relapsing MS as defined by clinical or imaging features.