Protocol

Diroximel fumarate (Vumerity®) treatment of relapsing-remitting multiple sclerosis (MS)

1 Scope

Treatment of patients with a diagnosis of multiple sclerosis by the MS team at Cambridge University Hospitals NHS Foundation Trust.

2 Purpose

To ensure the safe use and monitoring of diroximel fumarate (Vumerity®).

3 Introduction

Vumerity is indicated for treatment of people with 'active relapsing-remitting multiple sclerosis':

- Active relapsing-remitting MS is **normally** defined as at least two clinically significant relapses in the previous two years.
- NICE recognised that the current comparator drug, Dimethyl fumarate (Tecfidera), is in practice is offered to people considered to have 'active' disease with a single recent relapse of the presence of radiological activity, such as new MRI lesions, without a clinical relapse. The phrase 'normally defined' allows some room for clinical discussion.
- The marketing authorisation is for the treatment of adults with RR-MS; the NICE-TA794 is more restrictive, as above
- Patients with highly active RR-MS or rapidly evolving severe MS are not eligible for Vumerity® (or for Tecfidera®)

4 Undertaken by (staff groups)

Medical staff and nursing staff who are competent to prescribe and monitor diroximel fumarate.

5 Treatment

5.1 Eligibility and screening

Patients will have been assessed as eligible for treatment by a consultant neurologist in the disease modifying therapy clinic. **NICE technology appraisal guidance TA794 Diroximel fumarate for treating relapsing–remitting**

multiple sclerosis (2022) will be followed when assessing eligibility. Risks and benefits will have been discussed. Medications and co-morbidities will have been documented on Epic.

A neurologist and MS nurse discuss the benefits and risks of Vumerity® with the patient. When the patient has decided to start treatment the MS nurse sends a letter recording the discussion to the patient with a copy to GP (using smart text .VUMERITYCONSENT). A Blueteq form is completed.

Pre-treatment screening will have occurred in the outpatient clinic setting:

- Screening blood tests are sent as outlined in the Multiple Sclerosis (MS) disease modifying therapy (DMT) Initiation and Monitoring Standard Operating Procedure.
- Vaccine advice given as per Multiple Sclerosis (MS) disease modifying therapy (DMT) Initiation and Monitoring Standard Operating Procedure.
- Baseline expanded disability status scale (EDSS)
- Baseline MRI brain scan ordered (should be done within three months of starting treatment) if clinician feels appropriate to allow radiological monitoring of treatment efficacy
- Pregnancy, breast feeding and importance of contraception whilst on treatment discussed and documented. Animal studies have shown reproductive toxicity. Pregnancy should be avoided whilst taking Vumerity®.

5.2 Caution and contraindications

- Hypersensitivity to active substances
- Current suspected or confirmed PML (progressive multifocal leukoencephalopathy)
- Severe renal or severe hepatic impairment
- Pre-existing low lymphocyte counts – these require further investigation. A lymphocyte count below 0.5 x10^9/L is an absolute contraindication to starting Vumerity®
- Immunocompromised e.g. HIV, hepatitis B&C
- Severe active gastrointestinal disease
- Taking anti-neoplastic or immunosuppressive therapies
- Taking nephrotoxic drugs (e.g. diuretics, NSAIDs or lithium)

5.3 Dosage

The dose is commenced at a lower dose of 231mg twice daily for the first 28 days in order to reduce the incidence of side effects. The dose should then be increased to 462mg twice daily.

5.3.1 Common side effects

- Flushing (33% compared to 41% with Tecfidera) and feeling hot and/or itchy; consider adding aspirin 75 mg

- Gastroenteritis
- Gastrointestinal upset (nausea and vomiting, diarrhoea, abdominal pain, indigestion) 35% vs 49% with Tecfidera. Discontinuation rate of 0.8% vs 4.8% with Tecfidera.
- Lymphopenia and leucopenia
- Elevated liver enzymes

Please note there have been a very small number of cases of progressive multifocal leukoencephalopathy (PML) in patients on dimethyl fumarate who have not previously received natalizumab or other immunosuppression. These are mostly linked to patients with low lymphocytes counts below 0.5 for 6 months or more. Equivalent data is not yet available for diroximel fumarate; the same cautions apply.

Fanconi syndrome has also been reported with a medicinal product containing dimethyl fumarate in combination with other fumaric acid esters. It can occur with normal creatinine. Symptoms involve polyuria, polydipsia and proximal weakness. Urine dip shows proteinuria, glucosuria (with normal blood sugar), hyperaminoaciduria and phosphaturia.

5.4 Switching to diroximel fumarate from other therapies

For patients switching from interferon or glatiramer acetate, no wash out period is required prior to starting diroximel fumarate.

5.5 Switching from diroximel fumarate to other therapies

If the lymphocyte count is above 1.0, no wash out period is required. In general a lymphocyte count of >0.8 is recommended when starting other MS DMTs. The wash out period required to reach this varies from patient to patient, but about 50% will be in the lower limit of normal (0.91) by 12 weeks.

5.6 Stopping Vumerity when planning to conceive

The half- life of Vumerity is approximately one hour and no circulating Vumerity is present at 24 hours in the majority of individuals. We advise a one month wash out period given the documented teratogenicity.

5.7 Prescription and supply

- Patient consented to homecare and alert added to patient record.
- MS nurse informs MS team administrator of new starter therapy.
- Blueteq form completed by MS team administrator.
- Initiation homecare prescription (231mg twice daily 28 days, 0 repeats) and registration forms completed. (Extension of 7 days titration as per SPC to improve tolerability of side effect profile).
- Continuation homecare prescription (462mg twice daily, 5 repeats) completed for first six months.

- Continuation homecare prescriptions for patients on treatment > 6 months 462mg twice daily, 2 x 56 supplied, 2 repeats).
- Prescriptions collected by CUH Homecare team for processing.
- Anticipate four week turnaround time from prescription signing to patient receiving treatment.
- Upon registration, the homecare company will contact the patient to arrange delivery.
- A signature is required for delivery.
- If the patient does not consent to homecare, the patient will need to agree to collect treatment from CUH Outpatient Pharmacy.

5.8 Patient counselling

MS nurse reviews patient in MS nurse clinic (may be a remote consultation) to complete the consent process, explain about Homecare and initiate treatment. Patient is given Vumerity® tip sheet for dealing with side effects.

The importance of regular blood tests and clinic appointments will be discussed in clinic.

Patients are advised to take diroximel fumarate with food in order to improve tolerability with respect to flushing or gastrointestinal adverse events (does not affect exposure significantly).

MS nurse sends Vumerity smart-text consent letter to patient and GP at the time the nurse asks the doctor (via the MS team administrator) to prescribe the drug.

6 Follow up and monitoring

- **Outpatient appointments** to assess side effects, drug compliance and disease activity:
  - By MS nurse at month 3 and month 12.
  - Seen by consultant neurologist at month 24.
  - After month 12:
    - If the lymphocyte count at month 12 is $<1.0 \times 10^9$/L, the patient should have a monitoring FBC every 3-6 months
    - If the lymphocyte count at month 12 is $\geq 1.0 \times 10^9$/L the patient is seen twelve-monthly, alternating between the MS nurse and consultant.
- **Monitoring**:
  - FBCs checked at month 3 and 9, and then 3-6 monthly depending on the lymphocyte count.
  - LFTs and U&Es at month 3 and then 6 monthly
  - If at any time point the lymphocyte count is $<0.5 \times 10^9$/L the patient should have a repeat FBC after three months. **If the lymphocyte count is sustained $<0.5 \times 10^9$/L for six months the patient will be seen by the neurologist and treatment will be stopped**.

- If the lymphocyte count is very low on a single test (in the region of 0.1 x10^9/L or below) an urgent repeat will be performed and if confirmed treatment stopped.
- To date there have been a very small number of cases of PML in patients on dimethyl fumarate (Tecfidera®) who have not previously received natalizumab or other immunosuppression. If PML is suspected, an MRI brain should be performed immediately and treatment with diroximel fumarate (Vumerity®) should be suspended until PML has been excluded.
- Treating clinician to consider a re-baseline MRI brain scan (and/or spine if spinal dominant disease) after 12 months of treatment to assess radiological efficacy if this would lead to consideration of treatment escalation

6.1 Stopping criteria

- Development of secondary progression
- EDSS 7.0 i.e. loss of ambulation for greater than six months
- Unacceptable adverse effects
- Allergic reaction to diroximel fumarate
- Pregnancy and breast feeding
- Sustained reduction in lymphocyte count to less than 0.5x10^9/L for six months
- Persistent failure to keep booked appointments or adhere to blood test monitoring requirements

7 Monitoring compliance with and the effectiveness of this document

(a) Process for monitoring compliance and effectiveness

- Patients will be assessed every twelve months for continued eligibility for treatment by consultant neurologist or MS specialist nurse; this consultation may be remote
- Patients will agree before starting treatment to comply with treatment protocol, keep appointments and contact relevant health professionals in the event of changes in their underlying MS condition or suspected side effects
- Ongoing maintenance of database of patients offered treatment, undergoing treatment and stopping treatment, including reason for stopping treatment, will be kept by the MS specialist nurse to audit against NICE guidelines
- The MS team will be vigilant for post marketing safety data.

(b) Standards/ key performance indicators

- The audit department will request evidence of compliance with NICE guideline.
- Internal checks on safety, compliance and efficacy will be undertaken by the MS team.

8 References

National Institute for Health and Care Excellence (2022). Diroximel fumarate for treating relapsing–remitting multiple sclerosis
https://www.nice.org.uk/guidance/ta794

European Medicines Agency, SMPC for Vumerity
https://www.medicines.org.uk/emc/product/13087/smpc#gref

Equality and diversity statement

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