**Medication Request Guidelines**

**Dimethyl Fumarate**

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>HICL</th>
<th>GCN</th>
<th>Exception/Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIMETHYL FUMARATE</td>
<td>TECFIDERA</td>
<td>40168</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Guidelines for Use**

1. Is the patient at least 18 years of age?
   - If yes, continue to #2.
   - If no, do not approve.
   **Denial Text:** See the denial text at the end of the guideline.

2. Does the patient have a diagnosis of relapsing-remitting multiple sclerosis (RRMS), secondary-progressive multiple sclerosis, or progressive-relapsing multiple sclerosis?
   - If yes, continue to #3.
   - If no, do not approve.
   **Denial Text:** See the denial text at the end of the guideline.

3. Has the patient tried glatiramer/Copaxone AND an interferon (Rebif or Avonex or Extavia or Betaseron)?
   - If yes, **Approve for 12 months by HICL for #2 capsules per day**.
   - If no, continue to #4.
   **Denial Text:** See the denial text at the end of the guideline.

4. Does the patient have contraindication/intolerance/allergy to glatiramer AND interferon, or is the patient physically unable to self-inject despite coaching by RN/RPh and a caregiver is not available or is unable or unwilling to give injections?
   - If yes, **Approve for 12 months by HICL for #2 capsules per day**.
   - If no, do not approve.
   **Denial Text:** See the denial text at the end of the guideline.

**Denial Text:** Our guideline for **Dimethyl Fumarate** requires patient age 18 years or older; a diagnosis of relapsing-remitting, secondary-progressive or progressive-relapsing multiple sclerosis; and a trial of Copaxone as well as Rebif, Avonex, Extavia or Betaseron; or the patient is unable to self-inject despite coaching by a nurse or pharmacist and the caregiver is not available or is unable or unwilling to give injections.

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RATIONAL
To ensure appropriate use aligned with FDA approved dosing and indication. Clinical trials only studied adult patients (appropriate dosing in pediatric patients is unknown).

FDA APPROVED INDICATIONS
Tecfidera is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

DOSES
The starting dose for Tecfidera is 120 mg twice a day orally. After 7 days, the dose should be increased to the maintenance dose of 240 mg twice a day orally.

Multiple sclerosis is an autoimmune inflammatory demyelinating disease of the central nervous system characterized by instances of disease exacerbation (relapses). Relapses cause acute neurologic dysfunction, which can last a minimum of 24 hours and peak over the course of several days or weeks. After the relapse subsides, patients may fully recover or have permanent residual impairments. In RRMS, relapses are clearly defined and the disease does not progress during the time between each relapse. Although there are other types of multiple sclerosis, RRMS is the most common.

<table>
<thead>
<tr>
<th>Type of MS</th>
<th>Description</th>
<th>% MS population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically Isolated Syndrome (CIS)</td>
<td>Single neurologic symptomatic attack compatible with MS. Clinically defined MS occurs in about 80% of patients who have demyelinating lesions on MRI.</td>
<td>MS Precursor</td>
</tr>
<tr>
<td>Relapsing Remitting MS (RRMS)</td>
<td>Clearly defined acute exacerbations, followed by partial or complete recovery of the deficits.</td>
<td>85%</td>
</tr>
<tr>
<td>Secondary Progressive MS (SPMS)</td>
<td>Initiates as RRMS before developing into a more steady disability progression, which may also include occasional relapses. The transition to SPMS generally occurs in people who have been living with RRMS for at least 10 years.</td>
<td>85% of RRMS patients</td>
</tr>
<tr>
<td>Primary Progressive MS (PPMS)</td>
<td>Progression of disability from onset without plateaus or remissions. Does not experience acute attacks.</td>
<td>10%</td>
</tr>
<tr>
<td>Progressive Relapsing MS (PRMS)</td>
<td>Continuous worsening neurologic function with occasional relapses.</td>
<td>5%</td>
</tr>
</tbody>
</table>

The safety and efficacy of Tecfidera was evaluated in two randomized, multi-national, double-blind, phase III trials. The first trial, CONFIRM, randomized 1400 adults with relapsing remitting multiple sclerosis (RRMS) to one of four groups: Tecfidera 240mg twice daily, Tecfidera 240mg three times daily, Copaxone 20mg daily, and placebo. The primary endpoint for CONFIRM was annualized relapse rate (ARR) at 2 years. Secondary endpoints included the proportion of patients with relapse at two years, disability progression at two years, number of new/enlarging hyperintense lesions on T2, and number of new/enlarging hypointense lesions on T1. Tertiary endpoints included a comparison of the relative benefits and risks of Tecfidera or Copaxone versus placebo and the number of gadolinium enhancing lesions. Approximately 29% of the patients had tried injectable therapy for RRMS before participating in the trial.

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The second trial, DEFINE, randomized 1200 adults with RRMS to one of three groups: Tecfidera 240mg twice daily, Tecfidera 240mg three times daily, and placebo. The primary endpoint for DEFINE was the proportion of patients with relapse at 2 years. Secondary endpoints included the ARR at 2 years, disability progression at two years, number of new/enlarging hyperintense lesions on T2 and number of gadolinium enhancing lesions. Approximately 40% of the patients had tried injectable therapy for RRMS before participating in the trial.

Tecfidera significantly reduced ARR and the proportion of patients with relapse in both studies. However only DEFINE found a significant difference in disability progression. The ability of Tecfidera to reduce the risk of relapse is 34-49%. Copaxone reduced the risk of relapse by approximately 30%. All three MRI parameters (number of new/enlarging hyperintense lesions on T2, number of new/enlarging hypointense lesions on T1, and number of gadolinium enhancing lesions) were shown to be significant for CONFIRM. DEFINE also found significance in both of its MRI data (number of new/enlarging hyperintense lesions on T2 and number of gadolinium enhancing lesions). Post hoc analysis did not find a difference in efficacy between Tecfidera and Copaxone in any of the clinical and MRI data except that Tecfidera had significantly less hyperintense lesions on T2.

Tecfidera may decrease lymphocyte counts. During the first year, mean lymphocyte counts decreased by approximately 30% and then remained stable. Four weeks after stopping Tecfidera, mean lymphocyte counts increased but did not return to baseline. Six percent (6%) of Tecfidera patients and <1% of placebo patients experienced lymphocyte counts <0.5x10⁹/L. The incidence of infections (60% vs. 58%) and serious infections (2% vs. 2%) was similar in patients treated with Tecfidera or placebo, respectively. Before initiation of therapy, it is recommended to check a recent complete blood cell count to identify patients with pre-existing low lymphocyte counts.

REFERENCES