Multifocal motor neuropathy (MMN)

Condition for which Ig has an established therapeutic role.

Specific Conditions	• Multifocal motor neuropathy with or without persistent conduction block
Indication for Ig Use	• First-line and maintenance therapy for multifocal motor neuropathy (MMN) • Relapse of multifocal motor neuropathy (MMN) patients within six months of commencement of trial off immunoglobulin therapy
Level of Evidence	Clear evidence of benefit (Category 1)
Description and Diagnostic Criteria	Multifocal motor neuropathy (MMN) is a relatively rare disorder characterised by slowly progressive, asymmetric, predominately distal limb weakness without sensory impairment. Weakness often begins in the arms and the combination of weakness, wasting, cramps and fasciculations may suggest a diagnosis of motor neuron disease. However, clinical examination may demonstrate that the pattern of weakness follows the distribution of individual nerves rather than a spinal segmental pattern. Investigations will typically show conduction block on nerve conduction studies. IgM anti-GM-1 antibodies have been reported in a large number of patients with MMN and provide confirmatory evidence but are not essential for the diagnosis.
Justification for Evidence Category	The Biotext (2004) review found six low-quality case studies or crossover randomised controlled trials (RCTs) with a total sample size of 68 patients. A possible benefit of intravenous immunoglobulin (IVIg) treatment in these patients was observed, although five studies were not controlled. Frommer and Madronio (2006) identified a Cochrane systematic review including four RCTs. Thirty-four patients were randomly assigned to IVIg or placebo. IVIg treatment was superior to placebo in inducing an improvement in muscle strength. There was a trend (p=0.08) to reduced disability. In 2013, Han et al published a double-blind placebo-controlled study of IVIg treatment in 44 MMN cases. Patients were randomised 1:1 to receive either double-blind treatment with IVIg followed by placebo for 12 weeks each, or the reverse. A significant difference (P = 0·005) in mean maximal grip strength was observed during IVIg treatment (increased 3.75 percent) compared to placebo (decline 31.4 percent) (Hahn et al, 2013). A further review by Leger (2014) described the results of four small to moderate sized unblinded long-term follow-up studies of both treated and treatment naïve cases. Improvement was demonstrated in up to 70 percent of cases in grip strength and Medical Research Council (MRC) scores, confirming that IVIg is the most useful agent for initial and maintenance treatment of MMN. Consensus statements assert that IVIg is the only safe treatment demonstrated to be effective in patients with MMN. It is recommended in those who have significant disability. Dose and monitoring is similar to chronic inflammatory demyelinating polyneuropathy (CIDP). IVIg therapy is usually long term, but the minimum effective dose for each patient should be sought. Plasma exchange and steroids are ineffective and may cause deterioration. Regular maintenance doses of IVIg are needed. The National Guideline Clearinghouse (European Handbook of Neurological Management, 2011) recommends IVIg as first-line treatment for definite MMN when disability is sufficient to warrant treatment. A trial of IVIg is not recommended for patients with exclusion criteria, or those without typical clinical or electrophysiological features, who are likely to have motor neuron disease (MND).
Diagnosis Requirements	A diagnosis must be made by a Neurologist.

Qualifying Criteria for Ig Therapy

First-line and maintenance therapy for multifocal motor neuropathy (MMN)

This indication should be used for new patients and those that have never trialled off from Ig therapy. For responding patients who have relapsed after weaning from Ig therapy please use Indication 2: **Relapse of multifocal motor neuropathy (MMN) patients within six months of commencement of trial off immunoglobulin therapy**.

- Multifocal motor neuropathy, with a typical clinical phenotype, usually with persistent motor conduction block

  AND

- Progressive motor weakness is demonstrated in the distribution of individual peripheral nerves

  AND

- Demonstration of disability as measured by an Overall Neuropathy Limitations Scale (ONLS) score of at least 2 points

IVIg should be used for a maximum of 4 months (induction plus 3 maintenance cycles) before determining whether the patient has responded. If there is no benefit after this treatment, IVIg therapy should be abandoned.

Review by a neurologist is required within 4 months of treatment and annually thereafter. Documentation of clinical efficacy is necessary for continuation of IVIg therapy.

For patients in remission on maintenance therapy, a trial of weaning leading to cessation should be considered. If the patient relapses, they may be eligible for further Ig therapy under Indication 2: **Relapse of MMN patients within six months of commencement of a trial off Ig therapy**. A subsequent trial of weaning leading to cessation might be considered after a further 2 years of Ig therapy.

Relapse of multifocal motor neuropathy (MMN) patients within six months of commencement of trial off immunoglobulin therapy

This indication should be used for responding multifocal motor neuropathy (MMN) patients who have relapsed within 6 months of commencement of a trial off immunoglobulin therapy. For new patients and those that have never trialled off from Ig therapy, please use Indication 1: **First-line and maintenance therapy for MMN**.

- Following a trial off Ig therapy, deterioration in motor weakness compared to the level of weakness at the last review in a patient who was previously stable while on Ig therapy

  AND

- An increased level of disability as measured by the Adjusted Overall Neuropathy Limitations Scale (ONLS) with an increase of at least one point compared to the score at the last review

  AND

- Relapse occurred following trial off therapy

IVIg should be used for a maximum of 4 months (induction plus 3 maintenance cycles) before determining whether the patient has responded. If there is no benefit after this treatment, IVIg therapy should be abandoned.

Review by a neurologist is required within 4 months of treatment and annually thereafter. Documentation of clinical efficacy is necessary for continuation of IVIg therapy.

For patients in remission on maintenance therapy, a trial of weaning leading to cessation should be considered. If the patient relapses, again within 6 months of commencement of a trial off Ig therapy, they may be eligible for further Ig therapy under this indication. A subsequent trial of weaning leading to cessation might be considered after a further 2 years of Ig therapy.

Exclusion Criteria

Presence of upper motor neuron signs
Marked bulbar involvement
Significant sensory impairment without an adequate alternative explanation
Diffuse symmetric weakness during the initial weeks

Review Criteria for Assessing the Effectiveness of Ig Use

First-line and maintenance therapy for multifocal motor neuropathy (MMN)

IVIg should be used for a maximum of 4 months (induction plus 3 maintenance cycles) before determining whether the patient has responded. If there is no benefit after this treatment, IVIg therapy should be abandoned.

Review by a neurologist is required within 4 months of treatment and annually thereafter. Documentation of clinical efficacy is necessary for continuation of IVIg therapy.

For patients in remission on maintenance therapy, a trial of weaning leading to cessation should be considered. If the patient relapses, they may be eligible for further Ig therapy under Indication 2: **Relapse of MMN patients within six months of commencement of a trial off Ig therapy**. A subsequent trial of weaning leading to cessation might be considered after a further 2 years of Ig therapy.

Clinical effectiveness of Ig therapy can be assessed by:

On review of the initial authorisation period

- Improvement in focal motor weakness in previously weak (but not end-stage) muscles

  AND

- Improvement in the level of disability as measured by the Adjusted Overall Neuropathy Limitations Scale (ONLS) of at least one point less than the qualifying score

On review of a continuing authorisation period

- Improvement in or stabilisation of weakness after previous evidence of deterioration in motor strength. It is acknowledged that very slow deterioration may occur over several years in stable patients

  AND

- Improvement in or stabilisation of disability as measured by the Adjusted Overall Neuropathy Limitations Scale (ONLS) score compared to the previous review score *(note: gradual deterioration of one point over several years may occur)*

  AND

- A trial of Ig weaning/cessation of Ig therapy is planned for patients who are clinically stable to identify those in remission, or a reason provided as to why a trial is not planned

Relapse of multifocal motor neuropathy (MMN) patients within six months of commencement of trial off immunoglobulin therapy

IVIg should be used for a maximum of 4 months (induction plus 3 maintenance cycles) before determining whether the patient has responded. If there is no benefit after this treatment, IVIg therapy should be abandoned.

Review by a neurologist is required within 4 months of treatment and annually thereafter. Documentation of clinical efficacy is necessary for continuation of IVIg therapy.

For patients in remission on maintenance therapy, a trial of weaning leading to cessation should be considered. If the patient relapses, again within 6 months of commencement of a trial off Ig therapy, they may be eligible for further Ig therapy under this indication. A subsequent trial of weaning leading to cessation might be considered after a further 2 years of Ig therapy.

Clinical effectiveness of Ig therapy may be assessed by:

On review of the initial authorisation period

- Improvement in focal motor weakness in response to 4 months of Ig therapy compared to muscle strength at the qualifying assessment following relapse

  AND

- Improvement in disability as measured by the Adjusted Overall Neuropathy Limitations Scale (ONLS) compared to the qualifying assessment at relapse

On review of a continuing authorisation period

- Improvement in or stabilisation of focal motor weakness as compared to the focal muscle strength at the previous review assessment

  AND

- Improvement in or stabilisation of disability as measured by the Adjusted Overall Neuropathy Limitations Scale (ONLS) compared to the previous review score (gradual deterioration of one point over several years is acceptable)

  AND

- A trial of weaning/cessation of Ig therapy are considered annually for patients who are clinically stable to identify those in remission, or a valid reason provided as to why a trial is not being planned or is contraindicated at this time

Dose

First-line and maintenance therapy for multifocal motor neuropathy (MMN)

- **Induction Dose (IVIg)** - 2 g/kg in 2 to 5 divided doses.
- **Maintenance Dose (IVIg)** - 0.4-1 g/kg, 2–6 weekly. The amount per dose should be titrated to the individual's response, up to a maximum dose of 2 g/kg in any 4-week period. This might be by small doses more frequently than fortnightly.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Refer to the current product information sheet for further information on dose, administration and contraindications.

Relapse of multifocal motor neuropathy (MMN) patients within six months of commencement of trial off immunoglobulin therapy

- **Induction Dose (IVIg)** - 1-2 g/kg in 2 to 5 divided doses.
- **Maintenance Dose (IVIg)** - 0.4–1 g/kg, 2–6 weekly. The amount per dose should be titrated to the individual's response. A maximum dose of 2 g/kg may be given in any 4-week period. This might be by smaller doses more frequently than fortnightly.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Refer to the current product information sheet for further information on dose, administration and contraindications.

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Generated on: 26 May 2026