Tizanidine (Zanaflex®)
for spasticity associated with MS or spinal chord injury/disease

Guidance No. 17

GENERAL GUIDANCE
The Gwent Partnership Medicines and Therapeutics Committee have endorsed this guidance for the Primary Care prescribing of tizanidine for spasticity. This document should be read in conjunction with the:

1. Summary of Product Characteristics (SPC or Data Sheet) for tizanidine available at:

1. Licensed indication
   Treatment of spasticity associated with multiple sclerosis (MS) or with spinal cord injury or disease.

2. Therapeutic use and background
   Treatment of spasticity and spasms in MS can be justified on the following grounds:
   - To reduce the pain and distress caused by their very presence.
   - Treatment may be an integral part of a wider plan of management, e.g. reducing the burden of care, through enabling appropriate seating to be provided and used, or through reducing the risk of pressure ulcers.
   - To prevent and manage joint contractures (fixed limitations on the range of movement available at a joint).

Tizanidine is an \( \alpha_2 \)-adrenergic receptor agonist. The SPC states it reduces pathologically increased muscle tone, including resistance to passive movements and alleviates painful spasms and clonus.

The November 2003 NICE CG8 on MS (http://www.nice.org.uk/page.aspx?o=94076) states under section 1.7.6 on spasticity and spasms that tizanidine should be one of the options (A = directly based on category I evidence) given only if treatment with baclofen or gabapentin is unsuccessful or side effects are intolerable.

In the NICE ‘full guideline’ (6.5.1 Spasticity and spasms) it states:
Three RCTs and two randomised crossover trials compared the effect of tizanidine to placebo. One of the RCTs reported beneficial effects on four of eight of the outcomes measures assessed, including a reduction in muscle-tone score. One of the randomised crossover trials also reported beneficial effects on the number of patients in whom spasticity improved. However, none of the other three trials reported any overall effect on any of the outcome measures assessed. One further RCT compared tizanidine to the active comparator diazepam. The results indicated no difference in the clinical symptoms between the groups, and that diazepam was better tolerated.

3. Contraindications
   - Hypersensitivity to tizanidine or any other component of the product (SPC section 6.1 has list of excipients).
   - The use of tizanidine in patients with significantly impaired hepatic function.
   - Concomitant use of tizanidine with fluvoxamine or ciprofloxacin.

4. Typical dosage regimen
   Initially 2mg daily as a single dose increasing according to response at intervals of at least 3 to 4 days in steps of 2mg daily (and given in divided doses) usually up to 24mg daily in 3 to 4 divided doses. The total daily dose should not exceed 36mg.
   Patients with renal impairment may require lower doses.

This Guidance should be used in conjunction with the Summary of Product Characteristics (SPC)
5. Clinically significant drug interactions
Concomitant use of tizanidine with fluvoxamine or ciprofloxacin (both CYP450 1A2 inhibitors) is contraindicated – clinically significant and prolonged hypotension may result along with somnolence, dizziness and decreased psychomotor performance.
Co-administration of tizanidine with other inhibitors of CYP1A2 such as some antiarrhythmics (amiodarone, mexiletine, propafenone), cimetidine, some fluoroquinolones (enoxacin, norfloxacin) and ticlopidine are not recommended. Tizanidine may potentiate the effect of antihypertensive drugs, including diuretics. It may also potentiate hypotension or bradycardia when used concurrently with β-blockers or digoxin.
Caution should be exercised when tizanidine is prescribed with drugs known to increase the QT interval.
Alcohol or sedatives may enhance the sedative action of tizanidine. Oral contraceptives have the potential to reduce the clearance of tizanidine.

Check in BNF Appendix 1 before co-prescribing any other drug.

6. Clinically significant adverse drug reactions

<table>
<thead>
<tr>
<th>Clinical condition or sign</th>
<th>Management</th>
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<tbody>
<tr>
<td>Dizziness/nausea</td>
<td>Reduce dose initially, <strong>stop drug and discuss if persistent</strong></td>
</tr>
<tr>
<td>Hypotension</td>
<td>May respond to dose reduction, <strong>stop drug and discuss if severe</strong></td>
</tr>
<tr>
<td>Hallucinations</td>
<td>May be self-limiting, <strong>stop drug and discuss if persistent</strong></td>
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<tr>
<td>Raised LFTs (reversible on stopping treatment)</td>
<td>Greater than three fold rise in ALT, Alk Phos (from upper limit of normal range) <strong>stop drug and discuss</strong></td>
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</tbody>
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7. Monitoring

<table>
<thead>
<tr>
<th>Monitoring parameters &amp; Frequency</th>
<th>Laboratory results</th>
<th>Action to be taken if abnormal result identified by GP</th>
</tr>
</thead>
<tbody>
<tr>
<td>LFTs when symptoms suggest i.e. unexplained nausea, anorexia or tiredness.</td>
<td>Serum levels of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) are persistently above three times the upper limit of normal range.</td>
<td><strong>Stop Drug and discuss</strong></td>
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8. Specialist centre contact information

If stopping the medication or needing advice – please contact:
- **Royal Gwent**
  - Dr Gareth Llewelyn
  - 01633 234453
- **Nevill Hall**
  - Dr Kenneth Dawson
  - 01873 732739

9. Role of Specialist Centre

➢ To initiate tizanidine, make any dosage adjustments and undertake baseline monitoring.
➢ To provide a patient information leaflet indicating the risks and benefits associated with tizanidine therapy.
➢ To confirm patient understanding and consent to treatment.
➢ To advise the patient on potential side effects (particularly symptoms suggestive of liver dysfunction such as unexplained nausea, anorexia or tiredness) and the action to be taken should any of these occur.
➢ To prescribe the first four months treatment and also to undertake the initial monthly monitoring of liver function tests for this period in all patients as recommended in the SPC.

10. Role of Primary Care

➢ To prescribe tizanidine in line with this guidance.

11. Additional advice/information

Any serious reaction to an established drug should be reported to CHM (MHRA) using the Yellow Card system.

12. Supporting documentation

Patient information leaflet