Mirogabalin for pain due to fibromyalgia

NIHR HSRIC ID: 10050

Lay summary

*Mirogabalin* is a new drug to treat pain associated with fibromyalgia. Fibromyalgia is a long-term condition that causes pain all over the body. Mirogabalin is taken by mouth once a day at bedtime. If licensed, mirogabalin may offer patients with fibromyalgia an additional treatment option.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

- Pain due to fibromyalgia – first line.

TECHNOLOGY

DESCRIPTION

Mirogabalin (DS5565; mirogabalin besylate) is a voltage-dependent calcium channel subunit alpha-2/delta-1 ligand intended for the treatment of pain associated with fibromyalgia. It is structurally related to gabapentin and pregabalin. In a phase III clinical trial, it is administered orally at 15mg once a day at bedtime. The intended treatment duration has not been reported.

Mirogabalin does not currently have Marketing Authorisation in the EU for any indication.

Mirogabalin is not currently in clinical development in the EU for any other indication.

INNOVATION and/or ADVANTAGES

If licensed, mirogabalin will offer an additional treatment option for patients with fibromyalgia.

DEVELOPER

Daiichi Sankyo Co.

AVAILABILITY, LAUNCH OR MARKETING

Currently in phase III clinical trials.

PATIENT GROUP

BACKGROUND

Fibromyalgia syndrome (FMS) is a common rheumatologic condition characterised by chronic widespread pain and reduced pain threshold, with hyperalgesia and allodynia. Associated features include fatigue, depression, anxiety, sleep disturbance, headache, migraine, variable bowel habits, diffuse abdominal pain, and urinary frequency. The effects of these symptoms vary from person to person and from day to day. Many people have flare-ups from time to time when their symptoms become suddenly worse. The pain associated with fibromyalgia is generally continuous, but can fluctuate in severity. It tends to be felt as diffuse aching or burning, often described as head to toe. Although the pathogenesis of fibromyalgia is remains unclear, current research indicates increasing evidence for peripheral and central hyperexcitability at the spinal or brainstem level, altered pain perception, and somatisation. The onset of fibromyalgia can be sudden or gradual, traumatic or non-traumatic.

Until recently, the diagnosis of fibromyalgia was made based on specific tender points in certain areas of the body. However, new guidelines were released in 2010 by the American College of Rheumatology to address concerns about the diagnostic criteria. The previous
criteria did not take into account other important symptoms, such as fatigue, sleep disturbance and cognitive dysfunction, and did not account for fluctuations in disease, symptom severity or effectiveness of new treatments. The current guidelines recommend that healthcare professionals should consider the following features when making a diagnosis: widespread pain lasting three months or more, fatigue and/or waking up feeling unrefreshed, and problems with thought processes such as memory and understanding (cognitive symptoms)\textsuperscript{7,8}.

### CLINICAL NEED and BURDEN OF DISEASE

Fibromyalgia is a common rheumatological illness; it is more common than rheumatoid arthritis and may be even more painful. Fibromyalgia is much more common in women, with females outnumbering males in a ratio of 9:1. The most common age group affected is between 45–60 years, though it can occur at any age, including children. There is no reported difference in frequency between ethnic or social groups\textsuperscript{6}.

The prevalence of fibromyalgia in the general population is estimated to be approximately 5.4% (95% CI 4.7% to 6.1%)\textsuperscript{9,a}. This equates to approximately 2,958,460 people in England.

In 2014-15, there were 3,968 admissions for fibromyalgia (M79.7) in England, resulting in 2,489 bed days and 4,124 finished consultant episodes\textsuperscript{10}.

### PATIENT PATHWAY

#### RELEVANT GUIDANCE

**NICE Guidance**

No relevant guidance.

**NHS England Policies and Guidance**

No relevant guidance.

**Other Guidance**

- The European League Against Rheumatism (EULAR). EULAR revised recommendations for the management of fibromyalgia. 2016\textsuperscript{11}.
- Scottish Intercollegiate Guidelines Network. Management of chronic pain (SIGN 136). 2013\textsuperscript{12}.
- The European League Against Rheumatism (EULAR). EULAR evidence-based recommendations for the management of fibromyalgia syndrome. 2007\textsuperscript{13}.

### CURRENT TREATMENT OPTIONS

There is currently no cure for fibromyalgia, however there are treatments and therapies available to help patients with specific aspects of the condition. These may include pharmaceuticals, but physical and other therapies are also important. Medications to help

\textsuperscript{a} The study used to generate this figure used a modification of the ACR (2010) preliminary diagnostic criteria for fibromyalgia, which relies on self-reported pain and somatic symptoms and was developed specifically for epidemiological studies.
with pain, sleep disturbance or depression associated with fibromyalgia may be offered. Typically these do not eradicate pain, but they may help to reduce symptoms to a level that will enable gentle physical activity and other rehabilitation therapies.

Drugs routinely offered and recommended by guidelines include:\n
- Amitriptyline – first line\(^b\).
- Serotonin-noradrenaline re-uptake inhibitors (e.g. duloxetine and milnacipran).
- Anticonvulsants (e.g. pregabalin and gabapentin).
- Opioids (e.g. Tramadol) – usually offered only after amitriptyline, serotonin-noradrenaline re-uptake inhibitor and anticonvulsant therapy, or in combination with these therapies\(^c\).

Non-pharmacological interventions recommended for reducing pain include:\n
- Exercise,
- Biofeedback,
- Cognitive behavioural therapies,
- Acupuncture,
- Hydrotherapy,
- Meditative movement,
- Mindfulness.

### Efficacy and Safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Status</th>
<th>Source of information</th>
<th>Location</th>
<th>Design</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02187471, mirogabalin vs pregabalin or placebo; phase III.</td>
<td>Daiichi Sankyo Co.</td>
<td>Ongoing.</td>
<td>Trial registry 16.</td>
<td>EU (not incl UK), USA, and other countries.</td>
<td>Randomised, placebo and active-controlled.</td>
<td>n=1,301 (planned); aged ≥18 yrs; fibromyalgia as defined by the 1990 American College of Rheumatology (ACR) criteria for fibromyalgia: widespread pain present for ≥3 months and pain in ≥11 of 18 specific tender point sites; must also meet the 2010 ACR criteria: widespread pain index (WPI) ≥7 and symptom severity (SS) scale score ≥5, or WPI 3 to 6 and SS scale score ≥9; symptoms have been present at a similar level for ≥3 months; no disorder that would otherwise explain the pain; average daily pain score (ADPS) of ≥4 on the 11-point numeric rating scale (NRS) over the past 7 days (based on completion of ≥4 daily pain diaries); documented evidence of a fundoscopic examination (with pupil dilation) within 12 mths prior to screening or at screening.</td>
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<tr>
<td>NCT02187159, mirogabalin vs pregabalin or placebo; phase III.</td>
<td>Daiichi Sankyo Co.</td>
<td>Ongoing.</td>
<td>Trial registry 17.</td>
<td>EU (incl UK), USA, and other countries.</td>
<td>Randomised, placebo and active-controlled.</td>
<td>n=1,270 (planned); aged ≥18 yrs; fibromyalgia as defined by the 1990 ACR criteria for fibromyalgia: widespread pain present for ≥3 months and pain in ≥11 of 18 specific tender point sites; must also meet the 2010 ACR criteria: WPI ≥7 and SS scale score ≥5, or WPI 3 to 6 and SS scale score ≥9; symptoms have been present at a similar level for ≥3 months; no disorder that would otherwise explain the pain; ADPS ≥4 on the 11-point NRS over the past 7 days (based on completion of ≥4 daily pain diaries); documented evidence of a fundoscopic examination (with pupil dilation) within 12 mths prior to screening or at screening.</td>
</tr>
<tr>
<td>NCT02146430, mirogabalin vs pregabalin or placebo; phase III.</td>
<td>Daiichi Sankyo Co.</td>
<td>Ongoing.</td>
<td>Trial registry 18.</td>
<td>EU (not incl UK), USA, and Canada.</td>
<td>Randomised, placebo and active-controlled.</td>
<td>n=1,294 (planned); aged ≥18 yrs; fibromyalgia as defined by the 1990 ACR criteria for fibromyalgia: widespread pain present for ≥3 months and pain in ≥11 of 18 specific tender point sites; must also meet the 2010 ACR criteria: WPI ≥7 and SS scale score ≥5, or WPI 3 to 6 and SS scale score ≥9; symptoms have been present at a similar level for ≥3 months; no disorder that would otherwise explain the pain; ADPS ≥4 on the 11-point NRS over the past 7 days (based on completion of ≥4 daily pain diaries); documented evidence of a fundoscopic examination (with pupil dilation) within 12 mths prior to screening or at screening.</td>
</tr>
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</table>

\(^b\) Expert personal communication.
<p>| Schedule | Randomised to miogabalin 15mg oral once daily at bedtime; or miogabalin 15mg oral twice daily (titrated from 15mg once daily after 1 week, during the first week subject will take placebo in the morning); or pregabalin 150mg oral twice daily, one in the morning and at bedtime (during the first week of blinded-treatment, subjects will take one pregabalin 75mg capsule in the morning and one pregabalin 75mg capsule at bedtime); or placebo, taken orally in the morning and one at bedtime | Randomised to miogabalin 15mg oral once daily at bedtime; or miogabalin 15mg oral twice daily (titrated from 15mg once daily after 1 week, during the first week subject will take placebo in the morning); or pregabalin 150mg oral twice daily, one in the morning and at bedtime (during the first week of blinded-treatment, subjects will take one pregabalin 75mg capsule in the morning and one pregabalin 75mg capsule at bedtime); or placebo, taken orally in the morning and one at bedtime | Randomised to miogabalin 15mg oral once daily at bedtime; or miogabalin 15mg oral twice daily (titrated from 15mg once daily after 1 week, during the first week subject will take placebo in the morning); or pregabalin 150mg oral twice daily, one in the morning and at bedtime (during the first week of blinded-treatment, subjects will take one pregabalin 75mg capsule in the morning and one pregabalin 75mg capsule at bedtime); or placebo, taken orally in the morning and one at bedtime |
| Follow-up | Active treatment for 13 wks. | Active treatment for 13 wks. | Active treatment for 13 wks. |
| Primary outcome/s | ADPS. | ADPS. | ADPS. |
| Secondary outcome/s | Patient global impression measure; Fibromyalgia Impact Questionnaire (FIQ); Multidimensional Fatigue Inventory (MFI-20); Hospital Anxiety and Depression Scale (HADS); Short Form 36 (SF-36) questionnaire; quality of life as assessed by EuroQoL Instrument 5 Domains (EQ-5D); pain associated sleep interference as assessed by the average daily sleep interference score (ADVIS); and the Medical Outcomes Study (MOS) Sleep Scale; Brief Pain Inventory Short Form (BPI-SF); proportion of days a rescue medication was used; adverse events (AEs). | Patient global impression measure; FIQ; MFI-20; HADS; SF-36 questionnaire; quality of life as assessed by EQ-5D; pain associated sleep interference as assessed by ADVIS and MOS Sleep Scale; BPI-SF; proportion of days a rescue medication was used; AEs. | Patient global impression measure; FIQ; MFI-20; HADS; SF-36 questionnaire; quality of life as assessed by EQ-5D; pain associated sleep interference as assessed by ADVIS and MOS Sleep Scale; BPI-SF; proportion of days a rescue medication was used; AEs. |
| Expected reporting date | Estimated study completion date reported as Jan 2017. | Estimated study completion date reported as Mar 2017. | Estimated study completion date reported as Mar 2017. |</p>
<table>
<thead>
<tr>
<th><strong>Trial</strong></th>
<th>NCT02234583, mirogabalin 15mg once daily vs twice daily; phase III extension.</th>
<th>NCT02496884, mirogabalin vs placebo; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sponsor</strong></td>
<td>Daiichi Sankyo Inc.</td>
<td>Daiichi Sankyo Inc.</td>
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<td><strong>Status</strong></td>
<td>Ongoing.</td>
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<td>Trial registry16.</td>
<td>Trial registry17.</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>EU (incl UK), USA, and other countries.</td>
<td>USA only.</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Non-randomised.</td>
<td>Randomised, placebo-controlled.</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>n=2,091 (planned); completed participation (i.e. completed the End-of-Tapering visit) in a preceding study of DS 5565 in fibromyalgia (NCT02187471; NCT02187159; NCT02146430); not experienced any significant safety issues during the preceding study that, in the investigator's judgment, would adversely impact the subject's well-being in the long-term extension. Newly diagnosed patients: aged ≥18 yrs; fibromyalgia as defined by the 1990 ACR criteria for fibromyalgia: widespread pain present for ≥3 months and pain in ≥11 of 18 specific tender point sites; must also meet the 2010 ACR criteria: WPI ≥7 and SS scale score ≥5, or WPI 3 to 6 and SS scale score ≥9; symptoms have been present at a similar level for ≥3 months; no disorder that would otherwise explain the pain; ADPS ≥4 on the 11-point NRS over the past 7 days (based on completion of at least 4 daily pain diaries); documented evidence of a fundoscopic examination (with pupil dilation) within 12 mths prior to screening or at screening.</td>
<td>n=60 (planned); aged ≥18 yrs; estimated creatinine clearance between 15-59ml/min; meeting the 2010 ACR criteria: WPI ≥7 and SS scale score ≥5, or WPI 3 to 6 and SS scale score ≥9; symptoms have been present at a similar level for ≥3 mths; no disorder that would otherwise explain the pain; ADPS ≥4 on the 11 point NRS for ≥7 days; no other severe pain that might impair the assessment of neuropathic pain.</td>
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<td><strong>Schedule</strong></td>
<td>Patients receive mirogabalin15mg oral once daily at bedtime; or mirogabalin 15mg oral twice daily, once in the morning and once at bedtime.</td>
<td>Patients with moderate chronic kidney disease are randomised to mirogabalin 7.5mg oral twice daily, or placebo oral twice daily. Patients with severe chronic kidney disease are randomised to mirogabalin 7.5mg oral once daily, or placebo oral once daily.</td>
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<tr>
<td><strong>Follow-up</strong></td>
<td>Active treatment for 52 wks.</td>
<td>Active treatment for 13 wks, follow up for 4 wks.</td>
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<tr>
<td><strong>Primary outcome/s</strong></td>
<td>AEs; number of subjects experiencing an abnormal value of a clinical laboratory test, both up to wk 52.</td>
<td>AEs up to week 13.</td>
</tr>
<tr>
<td><strong>Secondary outcome/s</strong></td>
<td>ADPS; ADSIS; Patient Global Impression of Change (PGIC); HADS; EQ-5D; SF-36; physical examination; ECG; the Columbia-Suicide Severity Rating Scale (C-SSRS); the Physician Withdrawal Checklist (PWC).</td>
<td>ADPS; PGIC.</td>
</tr>
<tr>
<td><strong>Expected reporting date</strong></td>
<td>Estimated study completion date reported as Aug 2017.</td>
<td>Estimated study completion date reported as Jun 2017.</td>
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</table>
## ESTIMATED COST and IMPACT

### COST

The cost of mirogabalin is not yet known.

A 56 capsule pack of pregabalin 150mg costs £38.64. Therefore 13 weeks of active treatment with pregabalin 150mg oral twice daily would cost £154.56.

### IMPACT - SPECULATIVE

#### Impact on Patients and Carers

- Reduced mortality/increased length of survival
- Other:
  - Reduced symptoms or disability
  - No impact identified

#### Impact on Health and Social Care Services

- Increased use of existing services
- Re-organisation of existing services
- Other:
  - Decreased use of existing services
  - Need for new services
  - None identified

#### Impact on Costs and Other Resource Use

- Increased drug treatment costs
- Other increase in costs:
  - None identified
- Other: uncertain unit cost compared to existing treatments.

#### Other Issues

- Clinical uncertainty or other research question identified: expert opinion suggests that if the intention is for potential patients to continue using mirogabalin beyond 13 weeks, then data is needed to at least 12 months before clinicians will take notice. Furthermore, all guidelines, and particularly recent EULAR guidelines, stress the need for non-medical therapies such as CBT and graduated exercise as well as medication in managing patients with fibromyalgia. Therefore these trials which look at drugs alone don’t reflect what should be done in practice and may underestimate benefit when all measures are used together.

- The requirement for potential patients to comply with both 1990 and 2010 ACR criteria (as detailed in the trial inclusion criteria) sets a high threshold as it is well known that many will fit one but not both sets as they are quite different. This may make it difficult to then...

  c Expert personal communication.
place the drug for those seen in practice who fulfil one criteria but not the other².

An expert also states, ‘I am not sure what the proposed place will be as there is no data yet. If equivalent to pregabalin, then the cheapest will find its way onto the formulary. If only mirogabalin is licensed but more expensive then I think pregabalin will win as it’s already so familiar to hospital pain teams. Some may go for gabapentin first (as they do now) if cheaper than pregabalin or mirogabalin in the absence of any comparative trials…In practice, the question will be what to do after amitriptyline and duloxetine/milnaciprin³.

REFERENCES