

## Milnacipran hydrochloride

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**Approved indication: fibromyalgia**  
**Joncia (Pierre Fabre Medicament)**  
**25 mg, 50 mg and 100 mg capsules**

Fibromyalgia is a chronic painful condition. It can reduce quality of life and is frequently associated with other symptoms such as fatigue, poor sleep and depressed mood. The non-drug management of fibromyalgia is important, but there is some evidence to support the use of drugs such as amitriptyline and duloxetine.

Like duloxetine, milnacipran inhibits the reuptake of noradrenaline and serotonin, but it has not been marketed as an antidepressant. Altering the neurotransmitters may inhibit pain signals, but the exact mechanism of action of milnacipran in fibromyalgia is unknown.

There have been several studies of milnacipran in fibromyalgia. Five of these were included in a systematic review. These trials involved 4138 patients, mostly female, randomised to take placebo or up to 200 mg milnacipran daily. In the analysis, 41% of patients obtained some pain relief (at least 30%) with milnacipran 100 mg daily, however 30% of the placebo group had the same outcome.<sup>1</sup> These response rates were not increased with a dose of 200 mg daily. Some of the trials used an endpoint which combined 30% pain relief with the patients' impressions of improvement. This composite endpoint was achieved by 27% of the patients taking milnacipran 100 mg and 25% of those taking 200 mg. The placebo response was 16–18%.<sup>1</sup>

Although fibromyalgia is a chronic disease, most of the studies in the review were short-term. The longest had a duration of 27 weeks. It randomised 888 patients and found that there was a statistically significant difference between milnacipran and placebo for several outcomes including pain, fatigue and function.<sup>2</sup>

Some of the studies had extension phases. In one of these, 198 patients who had completed three months of treatment could continue for a year. The 270 patients who had taken placebo were randomised to take milnacipran 100 mg, 150 mg or 200 mg. After a year the response rate ranged from 27.5% to 35.9%. There were improvements in pain, fatigue and sleep.<sup>3</sup>

In the systematic review, adverse events occurred in 86–87% of the milnacipran groups and 78% of the placebo group. Adverse events which were

significantly more frequent with milnacipran included nausea, vomiting, constipation, dizziness, hot flushes, hypertension, palpitations and tachycardia.<sup>1</sup> Pulse and blood pressure should be measured before and during treatment. Although there were few men in the studies, 23.9% developed dysuria and 8.7% reported testicular pain. Milnacipran is not recommended in pregnancy and is contraindicated during lactation.

Antidepressants, tramadol and St John's wort are contraindicated. Other drugs which may interact with milnacipran include lithium, parenteral digoxin, oral anticoagulants and the serotonin agonists ('triptans') used in the treatment of migraine.

A dose reduction may be needed in renal disease as milnacipran is mainly excreted in the urine. It has a half-life of about eight hours so twice-daily doses are recommended. The dose should be gradually titrated to 50 mg twice a day. This can be increased to 100 mg twice a day, but if there is no response after 12 weeks, treatment should stop. The drug should be gradually withdrawn over at least two weeks.

Another systematic review has analysed the trial data for milnacipran in comparison to amitriptyline and duloxetine. Although there were methodological problems, amitriptyline was superior for improving pain, fatigue and sleep. Milnacipran was superior to duloxetine for fatigue, but inferior for pain and sleep.<sup>4</sup>

A difficulty in assessing the effectiveness of milnacipran is that many patients dropped out of the trials. In the systematic review 34% of the patients taking milnacipran 100 mg dropped out, mainly because of adverse events, compared with 30% of the placebo group.<sup>1</sup> How the data from these patients are handled influences the efficacy results. In the 27-week trial 42% of the patients discontinued treatment. Depending on the analysis used, the response rates to milnacipran 100 mg could be 33.3% or 18.3%. The lower value is not statistically different from placebo.<sup>2</sup> It is also uncertain how much benefit milnacipran has beyond a possible effect on depression. In the clinical trials approximately 30% of the patients had a history of depression. In 2009 the evidence of efficacy was insufficient for milnacipran to gain marketing approval in Europe.

Only a minority of patients will benefit from milnacipran. Approximately nine need to be treated for one patient to get a 30% reduction in pain. However, for every seven patients treated with 200 mg, or 14 treated with 100 mg, one will have to stop milnacipran because of adverse events.<sup>1</sup>

**T** manufacturer provided the AusPAR.

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The Transparency score is explained in [New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.](#)

At the time the comment was prepared, information about this drug was available on the websites of the [Food and Drug Administration](#) in the USA, the [European Medicines Agency](#) and the [Therapeutic Goods Administration](#).