Medicines Adverse Reactions Committee

Meeting date	**3 July 2018**	Agenda item	3.2.3
Title	**Potential interaction between nefopam and tramadol**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active constituent	**Medicines**	**Sponsors**
Nefopam	Acupan tablet 30 mg	iNova Pharmaceuticals NZ Ltd
Tramadol	Arrow – Tramadol capsule 50 mg	Teva Pharma NZ Ltd
	Durotram XR modified release tablet 100, 200, 300 mg	iNova Pharmaceuticals NZ Ltd
	Tramal capsule 50 mg, solution for injection 50 mg/ml, 100 mg/2ml, oral drops 100 mg/ml	Seqirus NZ Ltd
	Tramal SR modified release tablet 50, 100, 150, 200 mg	

Funding	Acupan 30 mg, Arrow-Tramadol 50 mg, Tramal SR 100, 150 and 200 mg
Previous MARC meetings	The potential interaction between these two medicines has not been discussed previously.
Prescriber Update	www.medsafe.govt.nz/profs/PUArticles/Sep2015/InteractionsSerotoninSyndrome.htm
Schedule	Prescription medicine
Usage data	See section 2.3
Advice sought	**The Committee is asked to advise whether:** – The data sheets should be updated regarding the risk of serotonin syndrome if nefopam and tramadol are used in combination or – The data sheet for nefopam should be updated with the general risk of serotonin syndrome if used concomitantly with other medicines that increase serotonin levels. – This topic requires further communication other than MARC's Remarks in *Prescriber Update*.

Table of Contents

1.0 PURPOSE

Medsafe has received a consumer query about a potential interaction between nefopam and tramadol. The data sheets for the two medicines do not include such an interaction. One mechanism of action for Acupan (nefopam) is inhibition of serotonin reuptake and the medicine is contraindicated for patients who are also treated with MAO-inhibitors. This suggests that nefopam may cause serotonin syndrome if used in combination with medicines that also increase the level of serotonin, such as tramadol. Serotonin syndrome is currently not listed as a risk of this combination in any of the data sheets involved.

Considering the potential risk of an interaction and the fact that NZ is one of few countries where nefopam is on the market, Medsafe considers that this safety concern should be reviewed by the MARC.

2.0 BACKGROUND

2.1 Indications, dosing and characteristics

2.1.1 Nefopam

Nefopam (Acupan) is a centrally acting analgesic with a rapid onset of action. The indication for the medicine is relief of acute pain, including post-operative, dental, musculoskeletal and acute traumatic pain. Acupan tablets contain 30 mg nefopam and the dosing is 1 to 3 tablets three times daily depending on response (1).

Nefopam is only available in a few countries including NZ, the UK and France. There is no central European approval through the EMA and the medicine is not available in the US or Canada.

Acupan is distinct from other centrally acting analgesics such as morphine, codeine, pentazocine and propoxyphene. Unlike the narcotic agents, Acupan has not been shown to cause respiratory depression. In addition, there is no evidence from pre-clinical research of habituation occurring with Acupan (1). Nefopam does not bind to opioid receptors, has no effect on platelets and does not induce an anti-inflammatory effect like the NSAIDs (2).

Common side effects of Acupan include nausea, nervousness, urinary retention, dry mouth and light-headedness. As with other drugs with anticholinergic properties, confusion and urinary retention can be a problem in the elderly. Nefopam can be fatal in overdose. Clinical features may include convulsions, hallucinations, agitation and tachycardia (3).

2.1.2 Tramadol

Tramadol is a centrally-acting synthetic analgesic with opioid-like effects even if not chemically related to opiates. Tramadol is indicated for relief of moderate to severe pain and is available as capsules 50 mg, modified release tablets 50, 75, 100, 150, 200 and 300 mg and as a solution for injection. The dosing of the capsules is 50 – 100 mg administered two or three times daily, and sometimes more often. The modified release tablets are to be taken once a day. The maximum daily dose should never exceed 400mg per day.

The analgesic effect of tramadol is dose-dependent, but the relationship between serum concentrations and analgesic effect varies considerably between individuals.

Apart from analgesia, tramadol may produce other symptoms similar to that of opioids including dizziness, somnolence, nausea, constipation, sweating and pruritus. Tramadol, however, causes significantly less respiratory depression than morphine (4).

Other adverse effects include for example dry mouth, dyspepsia, biliary spasm, palpitation, hallucinations, mood changes, dizziness, confusion, sleep disturbances, sexual dysfunction, urinary retention and less commonly bronchospasm, raised liver enzymes, seizures and nightmares (5).

Comments: Nefopam is only available in a few countries which affects the amount of data and new data available.

2.2 Mechanisms of action

2.2.1 Nefopam

The main site of action of nefopam appears to be in the central nervous system, both at the brain and spinal levels. *In vitro* experiments have shown nefopam to inhibit the re-uptake of various catecholamines (including noradrenaline, serotonin and dopamine). It is possible that the mechanism of action of nefopam is at least in part by altering the levels of these neuromodulators in the brain and at the spinal level. Nefopam has been shown to have sympathomimetic and anticholinergic actions (1).

An additional mechanism of action is the effects on the glutamatergic pathway via modulations of calcium (inhibition of calcium influx) and sodium channels (blockage of voltage-sensitive sodium channels) that lead to decreased activation of postsynaptic glutamatergic receptors such as N-methyl-D-aspartate (NMDA) receptors, that are involved in the development of hyperalgesia (2).

2.2.2 Tramadol

The mode of action for tramadol is not completely known, although at least two complementary mechanisms have been suggested: binding to μ-opioid receptors by tramadol and its principle active metabolite O-desmethyltramadol, and inhibition of re-uptake of noradrenaline and serotonin (4).

Tramadol consists of 2 enantiomers with analgesic properties, both with different mechanisms of action. (+)-Tramadol and it metabolite O-desmethyltramadol (M1) act as selective mu-receptor agonists altering the release of nociceptive neurotransmitters. The mu activity of tramadol is around 10 fold less than that of codeine with the M1 metabolite having 300 times more affinity for mu receptor compared to its parent compound. Also (+)-tramadol inhibits serotonin reuptake and (-)-tramadol inhibits norepinephrine reuptake (6).

Both animal and human studies have shown that antinociception induced by tramadol is only partially antagonised by the opiate antagonist naloxone (4).

Comments: The mechanism of action for the two medicines is not completely known but partly similar. Both nefopam and tramadol have been shown to inhibit the reuptake of serotonin.

2.3 Usage

2.3.1 Nefopam

Nefopam may sometimes be preferred because alternatives are contraindicated or ineffective, or used as add-on therapy when pain is inadequately controlled. However there is little evidence of efficacy.

Very limited evidence is available for the effectiveness of nefopam in the treatment of persistent or chronic pain. Most published guidelines and reviews refer to the use of nefopam in the treatment of postoperative or acute pain.

A Cochrane Review from 2009 found that there was an absence of evidence of efficacy in treatment of acute postoperative pain in adults (7). Another Cochraine review from 2012 concluded that based on 2 small trials, which were both at high risk of bias, there was weak evidence that nefopam is superior to placebo in reducing pain in patients with rheumatoid arthritis (RA). In addition, the medicine has a significant side effect profile that may offset the benefits. Use of nefopam was not supported for use in treatment of patients with RA (8).

Nefopam has also been studied in prophylaxis and treatment of shivering and severe hiccups and has been suggested as an alternative in treatment of neuropathic pain (9).

The use of nefopam (number of prescriptions dispensed in a community pharmacy) in NZ is shown below:

Year	**2012**	**2013**	**2014**	**2015**	**2016**
Number of prescriptions	5 017	4 598	4 654	4 931	5 177

Acupan is a funded medicine.

2.3.2 Tramadol

Tramadol is a commonly used analgesic.

The use of tramadol (number of prescriptions dispensed in a community pharmacy) in NZ is shown below:

Year	**2012**	**2013**	**2014**	**2015**	**2016**
Number of prescriptions	329 111	374 516	401 682	427 745	455 587

Currently Arrow-Tramadol capsules 50 mg and Tramal SR 100, 150 and 200 mg are funded.

Comments: Management of nociceptive and/or neuropathic pain is based on the notion that two compounds (e.g., NSAID and opioid analgesic) may have additive effects if they target complementary pathways or mechanisms of a common clinical condition. Thus, it is possible to obtain the same pharmacological effect with two compounds each at a lower dose than is necessary to produce the same effect with either compound alone, thereby minimizing side effects associated with either compound.

As the mechanism of action for these two drugs are partially similar, treatment with the combination can be questioned. No publication on use of these two medicines together has been found. The article from Girard et al describes combination therapies involving nefopam, but none of them involves tramadol. In a recent Cochrane review of combination pharmacotherapy for the treatment of fibromyalgia, tramadol is included but not nefopam *(10)*. However, the combination may occur in clinical practice.

2.4 Serotonin syndrome

The potential identified risk is serotonin syndrome, caused by an interaction between nefopam and tramadol.

Serotonin syndrome is a toxic state caused mainly by excess serotonin within the central nervous system. It results in a variety of mental, autonomic and neuromuscular changes, which can range in severity from mild to life-threatening. The majority present within 24 hours, and most within six hours, of a change or initiation of a drug (11).

Patients will present with a triad of symptoms that range in severity. In mild cases, the predominating features are mild hypertension and tachycardia, mydriasis, diaphoresis, shivering, tremor, myoclonus, and hyperreflexia. Patients with a mild syndrome are usually afebrile. Mild cases may be misdiagnosed as general side effects of treatment.

Patients with a moderate syndrome usually have the above symptoms plus hyperthermia, hyperactive bowel sounds, horizontal ocular clonus, mild agitation, hypervigilance, and pressured speech. In severe cases, patients have all of the above symptoms plus severe hyperthermia, dramatic

swings in pulse rate and blood pressure, delirium, and muscle rigidity. In severe cases, complications may occur which may be fatal (12).

Serotonin syndrome may result from any combination of drugs that has the net effect of increasing serotonergic neurotransmission. The syndrome is classically associated with the simultaneous administration of two serotonergic agents, but it can occur after initiation of a single serotonergic drug or increasing the dose of a serotonergic drug in individuals who are particularly sensitive to serotonin. Episodes of serotonin syndrome involving a monoamine oxidase inhibitor may be more severe and more often lead to adverse outcomes, including death (11).

Severe serotonin syndrome is nearly always caused by a drug interaction involving two or more 'serotonergic' drugs, at least one of which is usually a selective serotonin reuptake inhibitor or monoamine oxidase inhibitor. Generally, drugs with two different mechanisms of action on serotonin must be present for a severe serotonin syndrome to develop (13). This publication also lists a number of medicines implicated in severe serotonin syndrome. Tramadol is one of them, but not nefopam.

Another mechanism for serotonin syndrome involves the inhibition of certain cytochrome P450 (CYP450) enzymes by a medicine resulting in accumulation of certain serotonergic drugs that are usually metabolized by these enzymes, for example tramadol (12).

Comments: Serotonin syndrome may be under reported as an adverse reaction, especially in less severe cases when the symptoms may be considered to be general adverse reactions of treatment.

2.5 Data sheets

2.5.1 Nefopam New Zealand

The data sheet for nefopam (iNova Pharmaceuticals NZ Limited) currently includes the following (1):

Under **Contraindications**: Acupan is contraindicated in patients with a history of convulsive disorders and should not be given to patients taking monoamine oxidase (MAO) inhibitors.

Under **Warnings and precautions**: Caution should be exercised when nefopam is administered concurrently with tricyclic antidepressants.

Under **Interactions**: Acupan should be used with caution in patients on tricyclic anti-depressants and is contraindicated in patients on MAO inhibitors.

The data sheet was last updated 29 Jan 2018.

2.5.2 Tramadol New Zealand

The data sheet for Tramadol Arrow was last updated 17 Sept 2017 and currently includes the following (4):

Under **Contraindications**: Contraindicated in patients who are taking MAO inhibitors or who have taken them within the last 14 days.

Under **Warnings and precautions:**
Serotonin syndrome (serotonin toxicity)
Tramadol is known to cause Serotonin syndrome when used concomitantly with other medicines that increase serotonin levels. The presence of another drug that increases serotonin by any mechanism should alert the treating physician to the possibility of an interaction. Signs of serotonin syndrome may be, for example, confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea. Withdrawal of the serotonergic medicines usually brings about a rapid improvement. Drug treatment depends on the nature and severity of the symptoms.

Under **Interactions**:

Use with other serotonergic agents

The presence of another drug that increases serotonin by any mechanism should alert the treating physician to the possibility of an interaction. Concomitant therapeutic use of tramadol and serotonergic medicines such as selective serotonin re-uptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see Section 4.3 Contraindications), tricyclic antidepressants and mirtazapine may cause serotonin toxicity. Serotonin syndrome is likely when one of the following is observed:

- Spontaneous clonus
- Inducible or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature >38 degrees celsius and inducible or ocular clonus

Withdrawal of the serotonergic medicines usually brings about a rapid improvement. Drug treatment depends on the nature and severity of the symptoms.

Use with MAO inhibitors

Tramadol should not be used in patients who are taking MAO inhibitors or who have taken them within the last fourteen days, as tramadol inhibits the uptake of noradrenaline and serotonin.

The data sheet for Tramadol Hydrochloride from AFT Pharmaceuticals includes the same information as above (14). The data sheet was updated 21 August 2017. This product is not available but has a data sheet.

The data sheet for Sequirus tramadol includes the same information under Contraindications and Interactions, but not the part under Warnings and precautions (15). This data sheet was updated 18 Feb 2018.

2.5.3 Nefopam UK

The data sheet for Nefopam Hydrochloride (Meda Pharmaceuticals Ltd) currently includes the following information (16):

Under **Contraindications**: Nefopam Hydrochloride is contraindicated in patients with a history of convulsive disorders and should not be given to patients taking monoamine oxidase (MAO) inhibitors.

Under **Interactions**: Caution should be exercised when Nefopam Hydrochloride is administered concurrently with tricyclic antidepressants.

Comments: The data sheet for Acupan includes warnings when used together with tricyclic antidepressants or MAO inhibitors, but not a general warning to alert the doctor about the risk of serotonin syndrome if nefopam is used together with another drug that increases serotonin by any mechanism.

3.0 SCIENTIFIC INFORMATION

3.1 Published literature

No publication has been found on the combination of nefopam and tramadol.

No publication has been found linking nefopam to serotonin syndrome. This includes a lack of publications exploring risks for patients who are treated with nefopam and tricyclic antidepressants or MAO inhibitors.

However, there are publications regarding serotonin syndrome in relation to treatment with tramadol.

3.1.1 Beakley BD, Kaye AM et al, 2015 (6)

This is an overview of serotonin syndrome and tramadol, specifically looking at tramadol's pharmacology and risk factors for serotonin syndrome.

Data indicates that the incidence of serotonin syndrome is increasing with the widespread use of serotonergic drugs in practice, for example tramadol. Serotonin syndrome is associated with the use of serotonergic drugs. These include drugs influencing serotonin uptake, metabolism, synthesis, release, and serotonin receptor activity and also drugs with the ability to interfere with cytochrome P450 metabolism, specifically CYP2D6 and CYP3A4.

The authors conclude that physicians should be aware of tramadol as a potential single agent cause for serotonin syndrome. While overdose is a common cause for this adverse effect, as a single agent there is also the concern for patients with impaired metabolism of tramadol and/or deficient serotonin uptake.

3.2 Vigibase

In Vigibase there are 64 reports concerning the combination of nefopam and tramadol and nervous system disorders. In 17 of these, the reported reaction is dizziness. [redacted] There are 55 reports on psychiatric disorders with the combination in Vigibase. Of these 36 relates to confusion and 12 to hallucinations.

3.3 [redacted]

[redacted]

3.4 Company reports

[redacted]

[redacted]

3.5 CARM data

No cases of a potential interaction between nefopam and tramadol have been reported to CARM.

In the data base there are 98 reports for nefopam, but none of them include tramadol, and none of the reactions are classified as serotonin syndrome. There are 286 assessed reports for tramadol, 10 of these regard serotonin syndrome but none of those include nefopam.

Comments: There is generally a lack of data about nefopam, and no evidence regarding nefopam in combination with tramadol leading to a potential interaction. [redacted]

4.0 DISCUSSION AND CONCLUSIONS

The mechanism of action for nefopam and tramadol is not completely known but partly similar. Both nefopam and tramadol have been shown to inhibit serotonin reuptake.

New Zealand is one of few countries where nefopam is on the market. Therefore many other regulatory agencies will not be monitoring the combination treatment of nefopam and tramadol.

According to usage data, nefopam is used in NZ (approximately 5,000 prescriptions dispensed each year over the last 5 years), and tramadol is a commonly used analgesic (approximately 450,000 prescriptions in 2016 with increasing rates since 2012). The combination of the two is likely to be unusual, but there may be situations in clinical practice when both medicines are prescribed together. If so, there is a theoretical risk due to the mechanisms of action of the medicines that too high levels of serotonin are obtained, which could lead to serotonin syndrome.

However, this has not been confirmed by reported cases. [redacted]
There is generally a lack of data about nefopam, and no evidence regarding nefopam in combination with tramadol leading to a potential interaction.

Therefore it is hard to argue a direct addition of the interaction to the data sheet for Acupan.

Another option is to add a general text in the data sheet for Acupan about usage together with serotonergic agents, for example in line with the following:

Warnings and precautions:
Serotonin syndrome (serotonin toxicity)
Concomitant therapeutic use of nefopam and another drug that increases serotonin by any mechanism, such as tricyclic antidepressants and MAO inhibitors (see Section 4.3 Contraindications), may cause serotonin toxicity.

Such a text is present in a longer version in the data sheets for tramadol. A difference between the two medicines, is that contrary to nefopam, tramadol has been linked to serotonin syndrome.

A warning and a contraindication is in place for use of nefopam in relation to tricyclic antidepressants and MAO inhibitors. A general warning is considered appropriate as there are more classes of medicines increasing the level of serotonin.

5.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- The data sheets should be updated regarding the risk of serotonin syndrome if nefopam and tramadol are used in combination or
- The data sheet for nefopam should be updated with the general risk of serotonin syndrome if used concomitantly with other medicines that increase serotonin levels.
- This topic requires further communication other than MARC's Remarks in *Prescriber Update*.

6.0 ANNEXES

1. Teva Pharma NZ Ltd report [confidential]

7.0 REFERENCES

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15. Sequirus NZ Ltd. Tramal SR NZ data sheet 2018 [10 May 2018]. Available from: http://www.medsafe.govt.nz/profs/Datasheet/t/TramalcapSRtabinjoraldrops.pdf.

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