

WSIB RESTRICTED
Please check with your manager before sharing this document externally

Frequently Asked Questions About Aripiprazole

Abstract: This is a question and answer document about Aripiprazole/Abilify.
Title: Aripiprazole, Abilify, FAQ, questions and answers; Health Services Division, drug formulary, status update; medication indication, formulary; drug updates; medication update; side effects; pain treatment, sleep disorders; abilify prescription renewal; abilify entitlement renewal
Last updated: 04/25/2013 11:11:22 AM **Contact:** [Tina Parasitinos](#)
Author: [Tina Parasitinos](#) **Feedback:** [Click on your feedback](#)

Questions and Answers - for internal use only

1. How does Abilify® compare to other second-generation antipsychotics on WSIB formularies in terms of efficacy?

Abilify® is a second-generation antipsychotic (SGA) which is thought to work via agonist activity at the dopamine D2 and serotonin 5-HT1A receptors, and antagonist activity at the serotonin 5-HT2A receptors. SGAs available on WSIB formularies with similar mechanisms of action include olanzapine, quetiapine, and risperidone. Based on available comparative trials, aripiprazole has not been shown to be more effective than other second-generation antipsychotics.

2. What alternative antipsychotics are available on WSIB formularies and how do they compare in terms of side effects?

Various antipsychotic medications are available on the psychotropic formulary. They can be divided broadly into two groups -- first-generation antipsychotics (sometimes referred to as "typical" antipsychotics) and second-generation antipsychotics (sometimes referred to as "atypical" antipsychotics). Examples of first generation antipsychotics (FGA) listed on formulary include haloperidol, perphenazine, loxapine, and chlorpromazine. Examples of SGAs listed on formulary include risperidone, olanzapine, and quetiapine.

Clinically, both groups of antipsychotics are effective in reducing psychotic symptoms. A recent critical overview of antipsychotic evidence suggested that FGAs and SGAs may not differ significantly in overall efficacy or safety. FGAs are associated with higher rates of extrapyramidal side effects compared to certain SGAs. The SGAs differ from each other considerably in pharmacology and in side effect profiles. A summary of the efficacy and side effects of FGAs and SGAs can be found in table 1 below.

Table 1: Comparison of First- and Second Generation Antipsychotic Efficacy and Side Effects

	Olanzapine	Quetiapine	Risperidone	Haloperidol	Perphenazine	Chlorpromazine
Efficacy						
↓ positive symptoms	+++	++	+++	+++	+++	+++
↓ negative symptoms	+	+	+	+	+	+
Relapse (1 yr)	+++	?	+++	++	++	++
Adverse Effects						
anticholinergic	+	0	0	0	++	+++
cardiac repolarization	0	0	0	0	0	++
hypotension	++	++	+++	+	++	+++
hyper-prolactinemia	+	0	++	++	++	++
Type 2 diabetes	++	+	+	+	+	+
sexual dysfunction	++	+	++	++	++	+++
weight gain	+++	++	+	0	+	++
EPS	+	0	++	++++	+++	++
NMS	+	+	+	+++	++	+

++++ = very high	++ = moderate	0 = negligible	NMS = neuroleptic malignant syndrome
+++ = high	+ = low	? = poorly defined	EPS = extrapyramidal syndrome

¹ adapted from Gardner, DM et al. CMAJ 2005; 172:1703-11

3. Can aripiprazole be approved for the treatment of pain?

Aripiprazole should not be approved for the treatment of pain in injured/ill workers. There are no randomized controlled trials demonstrating efficacy of aripiprazole in treating pain of any type.

4. Can aripiprazole be approved for the treatment of sleep disorders?

Aripiprazole should not be approved for the treatment of sleep disorders in injured/ill workers. There are no randomized controlled trials demonstrating efficacy of aripiprazole in treating sleep disorders.

5. What are the treatment options for workers diagnosed with a sleep disorder secondary to a work-related injury/illness?

Various guidelines have been published reviewing the evidence in the treatment of insomnia^{1,2}. The following agents are listed on WSIB formularies and have been recommended as effective:

- First-line: zopiclone, temazepam
- Second-line: amitriptyline, trazodone, doxepin
- Third-line: L-tryptophan

1. Guideline for Adult Insomnia.

(see http://www.topalbertadoctors.org/informed_practice/clinical_practice_guidelines/complete%20set/insomnia/adult_insomnia_pda.pdf)

2. Schulte-Rodin, S et al. Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med 2008; 4:487-504.

6. What happens to my client who is currently receiving Abilify paid by the WSIB whose claim comes up for renewal?

Payment for Abilify® will continue for workers who were approved for entitlement prior to the effective date. Brand new requests for Abilify will not be approved. For claims whose Abilify entitlement comes up for renewal, it is expected that professional judgment will be exercised to determine if the worker.

Aripiprazole

Health Care Advice: Medications

WSIB RESTRICTED
Please check with your manager before sharing this document externally.

Title: **Frequently Asked Questions About Botox**

Abstract: This is a question and answer document about Botulinum toxin type A (e.g., Botox).

Tags: botox; Botox; botulinum toxin type A; frequently asked questions; FAQ; BTX-A therapy; cervical dystonia treatment; migraine treatment; headache treatment; botox treatment renewal; Drug Benefits Program; health care advice; medication; drug; best practices; WSIB Drug Formularies; Health Services Division; request for botox payment; payment process for botox

Last updated: 04/25/2013 11:14:19 AM

Contact: [Sumeet Sidhu](#)

Author: [Sumeet Sidhu](#)

Feedback: [Give us your feedback](#)

Questions and Answers - for internal use only

1. If a request is made to review a case on the merits and justice of Botulinum toxin type A (BTX-A) treatment, what should I consider in trying to determine if I should authorize its use?

All new requests for BTX-A must be referred to the medical consultant. Medical consultants may consider payment for BTX-A therapy in cervical dystonia where specific conditions are met (see question # 2). Requests for BTX-A for the treatment of other conditions will not be approved.

2. Under which circumstances may the exceptional use of BTX-A be approved for the treatment of compensable cervical dystonia in an injured worker?

BTX-A may be approved for the treatment of cervical dystonia if the following conditions are met:

- Medical Consultant review is documented in the file
- Entitlement within the claim to a cervical spine injury is documented
- Clinical reports supporting the diagnosis (e.g. clinical findings of involuntary contraction of muscles, involuntary movements, and distorted cervical posturing)
- Regular documentation of efficacy by the prescriber (e.g. physical exam, pain scores, return to work, monitoring changes in medication use) to be on file
- EMG-guided administration is preferred, where possible.

3. How long can an injured worker continue to receive BTX-A treatments for cervical dystonia?

BTX-A treatments for cervical dystonia may be initially authorized for a maximum of three courses of treatment (9 months). This is in line with the available information from clinical trials. Requests to continue BTX-A treatment past 9 months must be referred to the medical consultant. Continuation of treatment will only be considered in cases where a worker has clearly benefitted from BTX-A treatment. Documentation of the worker's improvement, as well

as an ongoing treatment plan, is required from the treating physician before considering extension of treatment past 9 months.

Extension requests for BTX-A may be approved for a maximum of an additional 9 months. After that time, another review is required to determine ongoing entitlement to treatment with BTX-A. Reasons for approval of an extension request for BTX-A must be clearly documented in the claim file.

4. What alternative do we currently have on our formularies for the treatment of conditions other than cervical dystonia?

There are a wide variety of medications available on the WSIB formularies which meet the needs of the majority of injured workers. The heterogeneity of the conditions for which BTX-A has been used does not allow a simple summary of treatment alternatives. Particular alternatives will be dependent on the worker's condition(s) and treatment history.

5. Can BTX-A be approved for the prevention / treatment migraines or other headaches secondary to a cervical injury?

No, BTX-A will not be approved to prevention/treatment of migraine or other headaches. The available studies assessing the efficacy of BTX-A in migraine prophylaxis or headache prevention/treatment have produced inconsistent results. Conventional alternatives (e.g., divalproex sodium) appear to be just as effective as BTX-A in migraine prophylaxis. There is no good evidence available that BTX-A is effective in the prevention or treatment of chronic headache; thus, BTX-A should not be approved for headache of any type.

6. What happens to my client who is currently receiving BTX-A paid for by the WSIB?

Payment for BTX-A will continue for workers who were approved for entitlement prior to the effective date. Brand new requests for BTX-A will not be approved. For claims whose BTX-A treatment comes up for renewal, it is expected that you will use your professional judgment to decide if the worker has benefited from the medication and merits continued use.

[Formulary Status Update on Botox](#)
[Botox Request Payment Process](#)
[Health Care Advice: Medications](#)

WSIB RESTRICTED
Please check with your manager before sharing this document externally.

Title: Frequently Asked Questions About Buprenorphine Transdermal

Abstract: This is a question and answer document about Buprenorphine Transdermal/BuTrans.

Tags: Buprenorphine Transdermal; BuTrans; Suboxone; suboxone; BTDS; treatment of pain; treatment of opioid addiction; FAQ; frequently asked questions; Health Services Division; drug formulary; status update; medications; indication; formulary; drug updates; health care advice; morphine equivalent dose; BuTrans renewal

Last updated: 04/25/2013 11:15:51 AM

Contact: [Tina Papastavros](#)

Author: [Tina Papastavros](#)

Feedback: [Give us your feedback](#)

Questions and Answers - for internal use only

1. What is the difference between buprenorphine transdermal system (BTDS)/BuTrans® and sublingual buprenorphine (Suboxone®)?

BTDS/BuTrans® is a once-weekly transdermal formulation that contains only buprenorphine. It is indicated in the treatment of persistent moderate pain.

Suboxone® is a sublingual formulation that contains a combination of buprenorphine (a partial mu-opioid receptor agonist) and naloxone (a mu-opioid receptor antagonist). Naloxone is included in the formulation to deter intravenous misuse of the drug (naloxone will induce acute withdrawal if the drug is injected). Suboxone® has been studied extensively in opioid maintenance treatment for which it has received its official indication. There are no randomized controlled trials (RCTs) available that demonstrate the efficacy of Suboxone® in the treatment of pain and it is not currently approved for the treatment of pain of any kind by Health Canada.

2. Has BTDS been studied in the treatment of pain in individuals at high risk of abuse?

The use of BTDS in the treatment of pain in individuals at high-risk of abuse or dependence has not been investigated in a randomized controlled trial.

3. Should BTDS be approved for the treatment of opioid addiction?

BTDS has never been investigated in an RCT for the treatment of opioid maintenance and should not be approved for this use.

4. Is BTDS effective in treating pain in patients who have failed to respond or have not tolerated other opioids?

There is no evidence that BTDS is effective in treating pain in patients who have failed to respond to or tolerate other opioids. None of the four randomized controlled trials investigating the use of BTDS in chronic non-cancer pain specifically assessed its efficacy in opioid refractory or intolerant patients. Indeed, three of the trials either excluded individuals requiring moderate to high doses of opioids (who would be more likely refractory to opioids) or excluded individuals who were deemed opioid refractory. The fourth trial only included patients whose pain was already responding to another opioid. A summary of relevant inclusion or exclusion criteria are listed in Table 1 below.

Table 1: Inclusion / exclusion criteria in BTDS trials

Trial	Population	Inclusion or Exclusion criteria regarding opioid response
Gordon et al ¹	Low back pain	Excluded opioid resistant individuals
Gordon et al ²	Low back pain	Excluded opioid resistant individuals
Munera et al ³	Osteoarthritis of hip or knee	Excluded patients taking opioid doses greater than 90mg/day morphine equivalent and > 12 doses/day of short-acting opioids
Landau et al ⁴	Noncancer pain	Included ONLY patients whose pain was controlled by opioids

1. Gordon A, et al. Clin Ther 2010;32:844-60.
3. Munera C, et al. J Opioid Manage 2010;6:193-202
4. Landau CJ, et al. Clin Ther 2007;29:2179-93

5. What is the morphine equivalent dose of BTDS?

A morphine equivalent dose (MED) has not been established. Studies using different buprenorphine formulations, routes of applications, and pain models have suggested that it may be 25-100 times more potent than oral morphine.⁵ One analysis of prescription data suggested that an equipotent ratio of buprenorphine to oral morphine may be 1:110-115 (i.e., 1mg BTDS = 110-115mg oral morphine).⁶ According to these estimates, an injured worker prescribed BuTrans® 5mcg/hr (for a total of 120mcg/24h or 0.12mg/24hr) would be receiving the equivalent of 10mg/day oral morphine.

Nonetheless, there appears to be great individual variation and any equivalency estimates remain highly controversial.⁷

5. Kress, HG, et al. Eur J Pain 2009;13: 219-230.
6. Sittl R, et al. Clin Ther 2005; 27:225-237.
7. [RxFiles Q and A Summary: Buprenorphine Transdermal Patch\(170k, pdf\)](#)

6. Has BTDS been compared to fentanyl in the treatment of chronic noncancer pain?

No, BTDS has not been compared to fentanyl in the treatment of chronic noncancer pain. Fentanyl is a more potent opioid than BTDS and is indicated in the treatment of persistent moderate to severe pain in individuals who are already receiving opioid therapy at a total dose of at least 60mg/day Morphine Equivalents. As such, fentanyl should not be used in opioid-naïve individuals. BTDS is indicated in the treatment of moderate persistent pain. It can be prescribed in opioid-naïve individuals,

however.

7. Is there a 3-day BTDS patch available in Canada?

No, a 3-day formulation is not available in Canada. A 3-day BTDS formulation is marketed in Europe in strengths of 35, 52.5 and 70mcg/hr, however. The 3-day formulation has been investigated in three randomized trials that enrolled subjects with severe or very severe pain. The majority of subjects enrolled had pain of a malignant origin. Although the 3-day formulation appeared to be more effective than placebo, results reported were inconsistent.

The once-weekly BuTrans® is the only formulation marketed in Canada and is available in strengths of 5, 10, and 20mc/hr. It is not indicated in the treatment of severe pain.

8. What happens to my client who is currently receiving BuTrans® paid by the WSIB and his claim comes up for renewal?

Payment for BuTrans® will continue for workers who were approved for entitlement prior to the effective date. Brand new requests for BuTrans® will not be approved. For claims whose BuTrans® entitlement comes up for renewal, it is expected that you will use your professional judgment to decide if the worker has benefited from the medication and merits continued use.

Buprenorphine Transdermal
Health Care Advice: Medications

WSIB RESTRICTED
Please check with your manager before sharing this document externally.

Title: Frequently Asked Questions About Buprenorphine/Naloxone

Abstract: This is a question and answer document about Buprenorphine / Naloxone (Suboxone).

Tags: Suboxone; Naloxone; Buprenorphine; treatment of opioid dependence; opioid dependence; methadone alternative; methadone; approval Suboxone treatment; Suboxone and pain treatment; Suboxone renewal; non approved medication Suboxone; Buprenorphine; opioid; health care advice; best practices; WSIB Drug Formularies; drug formulary; drug indication; drug status update; Health Services Division

Last updated: 04/25/2013 11:18:35 AM

Contact: [Tina Papastavros](#)

Author: [Sumeet Sidhu](#)

Feedback: [Give us your feedback](#)

Questions and Answers about Buprenorphine / Naloxone (Suboxone) - for internal use only

1. I thought using Buprenorphine / Naloxone (Suboxone) instead of methadone to treat opioid dependence made maintenance treatment a lot easier and less complicated.

Suboxone has some advantages that might make it easier to prescribe or take than methadone. Namely, induction of therapy with Suboxone can be achieved more quickly and easily and it can be administered on a less-than-daily dosing schedule (in individuals requiring low dose therapy [$\leq 12\text{mg/day}$]). However, maintenance therapy for opioid dependence is more complicated than simply prescribing a medication. Medication dosing must be part of a program that also delivers supervised medical care and treatment of concurrent mental health and other substance use issues, along with counseling and supplementary services (e.g., employment support, education, and health promotion, etc.). As such, physicians prescribing Suboxone must be part of a program or team that is specially trained in treating substance use issues and providing treatment and support for the many accompanying medical and non-medical issues of opioid dependence.

2. Do doctors prescribing Suboxone need an "exemption" to do so?

To prescribe methadone, physicians must be exempted under section 56 of the *Controlled Drugs and Substances Act*. Currently, there is no requirement for an exception to prescribe Suboxone. The College of Physicians and Surgeons of Ontario (CPSO) recommends that physicians prescribing Suboxone take a buprenorphine prescribing course, complete a day of clinical observation, and participate in continuing medical education (CME) in dependence therapy. However, the Canadian Expert Drug Advisory Committee recognized that Suboxone's effectiveness in opioid treatment will be dependent on the delivery of maintenance programs that not only treat substance use issues but also provide support for concurrent medical and non-medical issue, and recommended that prescribing of Suboxone be limited to physicians with an exemption to prescribe methadone.

3. Won't Suboxone be a less expensive alternative to methadone maintenance treatment, since it is available in tablets that can be taken home?

There is no pharmacoeconomic evidence to suggest that the use of Suboxone would be a more cost-effective alternative for injured workers requiring treatment for opioid dependence. Suboxone doses must be observed by a healthcare professional for a minimum of two months. After two months, the appropriateness of take-home doses can be assessed. Take-home doses are not appropriate for everyone, so some workers could continue to require observed dosing of Suboxone. This is similar to the process for dispensing methadone. Drug costs associated with Suboxone can range from approximately \$6.00 to \$22.00 per day, depending on the dose.

4. If a worker has entitlement to opioid dependence therapy and a request is made to review a case on the merits and justice of Suboxone treatment, what should I consider in trying to determine if I should authorize its extraordinary use?

Methadone is the most widely studied and most widely used drug therapy for opioid dependence, and is considered the "gold standard" against which other treatments must be compared. Methadone maintenance therapy (MMT) is generally the first choice when deciding on a course of treatment. As outlined in the Formulary Update document, there is currently no evidence that Suboxone is superior to methadone for the treatment of opioid dependence (and may actually be less effective at retaining patients in treatment). However, there are certain circumstances in which the use of Suboxone may be warranted.

In cases where a request is made to review the file in order to determine whether authorization for extraordinary use is merited, the request should only be approved for claims in which at least one of the following specific criteria can be documented in the file:

- Hypersensitivity to methadone
- QT prolongation, or high risk of QT prolongation
- Failure of a prior trial of methadone
- Accessibility to methadone is an issue.

If none of the abovementioned criteria can be documented, the request for extraordinary use should not be approved.

5. Can Suboxone be approved for the treatment of pain?

No. There are no RCTs available that demonstrate the efficacy of Suboxone in the treatment of pain. Suboxone is not currently approved for the treatment of pain of any kind by Health Canada. Requests for Suboxone for any reason other than compensable opioid dependence will not be approved.

6. What happens to my client who is currently receiving Suboxone paid by the WSIB? What happens when his / her claim comes up for renewal?

Payment for Suboxone will continue for workers who were approved for entitlement prior to the

effective date. Brand new requests for Suboxone **will not** be approved. In claims in which Suboxone entitlement comes up for renewal, entitlement for continued use can be allowed if there is documented benefit (e.g., adherence to their treatment program) from Suboxone use.

Formulary Listing Decisions on Suboxone (Buprenorphine/Naloxone)

Health Care Advice: Medications

WSIB RESTRICTED
Please check with your manager before sharing this document externally.

Title: Frequently Asked Questions about Cannabinoids

Abstract: This is a question and answer document about Cannabinoids.

Tags: Cesamet; Marinol; Sativex; Cannabis; Cannabinoids; medication for treatment of pain; pain treatment drugs; drugs for pain treatment; medical marijuana; treatment of chronic non cancer pain; CNCP; fibromyalgia pain; neuropathic pain analgesics Drug Listing Decisions; Cannabinoids; FAQ; frequently asked questions; health care advice; medication best practices; renewal request for Cesamet; renewal request for Marinol; renewal request for Sativex; WSIB Drug Formularies; Health Services Division; Clinical Pharmacology Advisory Committee

Last updated: 04/25/2013 11:19:51 AM **Contact:** [Tina Papastavros](#)

Author: [Sumeet Sidhu](#) **Feedback:** [Give us your feedback](#)

Questions and Answers - for internal use only

1. Won't Cesamet, Marinol, or Sativex be more useful for workers than opioids since they have a different mechanism of action?

Based on the available evidence, there is no proven advantage to the use of cannabinoids over opioid medications for pain. As monotherapy, one clinical trial actually showed that a weak opioid (dihydrocodeine) was more effective and better tolerated than Cesamet. Cesamet and Sativex have never been investigated as add-on therapies. The one randomized, controlled trial of adjunctive Marinol in chronic pain only investigated the effects of a single dose of Marinol compared to a single dose of placebo. All three cannabinoids should be used with extreme caution in individuals on other sedating drugs. There is a significant risk of adverse effects associated with combining cannabinoids with medications such as opioids which are often used to treat pain in injured / ill workers.

2. Can Cesamet, Marinol, or Sativex be used to treat pain associated with back injuries?

Most back injuries (excluding spinal cord injuries) are musculoskeletal (MSK) in nature. None of the cannabinoids have ever been investigated specifically in the treatment of back pain. Thus, the cannabinoids will not be approved for use in MSK back pain injuries.

3. I thought that these drugs would be a better alternative to medical (smoked) marijuana. Can these medications be approved for workers who are denied smoked marijuana?

There is insufficient evidence from the medical literature to support the use of medical marijuana or the synthetic cannabinoids in the treatment of chronic non-cancer pain. Therefore, the synthetic cannabinoids are not necessarily substitutes for medical (smoked) marijuana. For medical marijuana, there are concerns about potential harm, particularly if the plant is smoked. Due to the lack of therapeutic evidence and the potential for harm, neither synthetic cannabinoids nor medical (smoked)

marijuana should be approved for chronic non-cancer pain (CNCP).

4. What alternative do we currently have on our formularies for the treatment of CNCP?

Various alternative drug classes are currently available on the WSIB formularies. They include:

Nociceptive pain analgesics

- NSAIDs (e.g., diclofenac, naproxen, ibuprofen, etc.)
- Cox-2 Inhibitors (celecoxib)
- Opioids (e.g., Tylenol 3®, codeine phosphate, Codeine Contin®).

Neuropathic pain analgesics

- Tricyclic antidepressants (desipramine, amitriptyline, nortriptyline, imipramine)
 - Anticonvulsants (e.g., gabapentin)
 - Opioids (e.g., Tylenol 3®, codeine phosphate, Codeine Contin®)
 - Serotonin Norepinephrine Reuptake Inhibitor (e.g., venlafaxine XR).
-

5. If cannabinoids have been shown to reduce pain in fibromyalgia, why are these medications not being authorized for treatment of this illness?

The drug Cesamet has been shown in only one small, 4-week clinical trial to have decreased fibromyalgia pain according to one measure (the Fibromyalgia Impact Questionnaire) as compared to placebo. However, Cesamet has never been compared with any other active drug in the treatment of fibromyalgia pain. Furthermore, there are no clinical practice guidelines recommending the use of any cannabinoid medication for fibromyalgia. Medications listed on the WSIB formularies that are recommended by guidelines because they have been demonstrated to reduce pain and often improve function include amitriptyline, fluoxetine, and moclobemide. The place in therapy (if any) of cannabinoids for fibromyalgia has not been established. These drugs will not be approved for the treatment of fibromyalgia pain due to the lack of substantive evidence of efficacy for this condition.

6. What happens to my client who is currently receiving Cesamet, Marinol, or Sativex paid for by the WSIB?

Payment for cannabinoids will continue for workers who were approved for entitlement prior to the effective date. Brand new requests for Cesamet, Marinol or Sativex will not be approved. For claims whose cannabinoid entitlement comes up for renewal, it is expected that you will use your professional judgment to decide if the worker has benefited from the medication and merits continued use.

[Formulary Listing Decisions on Cannabinoids](#)
[Health Care Advice: Medications](#)


Title: Frequently Asked Questions About Cipralex

Abstract: This is a question and answer document about Cipralex.

Tags: Cipralex; antidepressant; escitalopram; health care advice; medication; drug; best practices; WSIB Drug Formularies; Health Services Division; drug formulary; status update; medications; indication; frequently asked questions

Last updated: 07/31/2012 01:12:58 PM

Contact: [Tina Papastavros](#)

Author: [Tina Papastavros](#)

Feedback: [Give us your feedback](#)

Questions and Answers - for internal use only

1. What is the difference between citalopram and escitalopram (Cipralex®)? Didn't a meta-analysis find that escitalopram was better?

Citalopram (Celexa®) is a racemic compound comprised of two isomers – (S)-citalopram and (R)-citalopram. The (S)-citalopram isomer is believed to be responsible for most of the drug's antidepressant effect. Escitalopram (Cipralex®) is the chemical name given to the drug containing only the (S)-citalopram isomer. It was developed and marketed by the same company that makes citalopram (Celexa®) [but released after Celexa® came off patent].

Although a manufacturer sponsored study concluded that escitalopram was more effective than citalopram in a single meta-analysis of 9 randomized controlled trials, the effect size reported was small and the difference between the two drugs was not deemed clinically important. This study also had several methodological flaws which limited the validity of the results. The authors failed to describe whether they completed a standard examination and rating of the quality of the studies included (and whether any studies were excluded), did not report the results using intention-to-treat analysis, and employed a questionable definition of remission that may have biased the results.

Most other meta-analyses have concluded that there are no clinically important differences between escitalopram and citalopram (or other second generation antidepressants).

2. How does escitalopram compare to other second generation antidepressants (SGAs) listed on WSIB formularies?

A meta-analysis which looked at the comparative benefits and harms of second-generation antidepressants found NO substantial differences in the comparative efficacy and effectiveness of SGAs for the treatment of major depressive disorder. Results from direct and indirect comparisons indicate that clinical response and remission rates are similar among second-

generation antidepressants.

This meta-analysis also found that SGAs appeared to cause similar adverse events; however, the occurrence of specific adverse events differed amongst agents. For example, sexual dysfunction appeared to be lower with the use of bupropion compared to escitalopram and other SGAs. (See table 2 below for a more detailed comparison of adverse events.)

3. Which alternatives are listed on WSIB formularies for treating individuals who are diagnosed with work-related Major Depressive Disorder (MDD)?

Table 1 below lists antidepressants which are available on WSIB formularies to treat major depressive disorder caused by a work-related injury/illness.

Table 1: Antidepressants available on WSIB Formulary

SSRIs	SNRIs	Others
Citalopram (Celexa®)	Venlafaxine (Effexor®)	Bupropion (Wellbutrin®)
Sertraline (Zoloft®)		Mirtazapine (Remeron®)
Paroxetine (Paxil®)		
Fluoxetine (Prozac®)		
Fluvoxamine (Luvox®)		

Note: Tricyclic antidepressants (TCAs) are also available on WSIB formularies, however, second generation antidepressants (such as those listed above) are recommended over first generation agents (such as TCAs) because of their relatively favourable side effect profile and reduced risk of harm in overdose.

4. Is escitalopram (Ciprallex®) better tolerated than citalopram or other second generation antidepressants?

The incidence of serious adverse events, withdrawals, and non-serious adverse events did not differ significantly between escitalopram (Ciprallex®) and citalopram in any of the key studies. As seen in Table 2 below, the adverse event profile of escitalopram (Ciprallex®) is similar to other second generation antidepressants. Common side effects include nausea, headache, sleep disturbance and sexual dysfunction. Eleven studies assessed the risk for suicidality in patients treated with second-generation antidepressants. No particular drug had an excess risk compared to other SGAs. No evidence was found relating to the long-term (beyond 12 weeks) safety of escitalopram.

Table 2: Comparison of Antidepressant Adverse Events

Table 2: Comparison of Antidepressant Adverse Events¹

	Anti-cholinergic Effects	Sedation	Orthostatic Hypotension	Conduction Abnormalities	GI distress
Selective Serotonin Reuptake Inhibitors					
Citalopram	0	+	0	0	+
Escitalopram	0	0	0	0	+
Fluoxetine	0	0	0	0	+
Fluvoxamine	0	0	0	0	++
Paroxetine	+	+	0	0	+
Sertraline	0	0	0	0	++
Serotonin/Norepinephrine Reuptake Inhibitors					
Venlafaxine	+	+	0	+	++
Duloxetine (NOT LISTED on WSIB formularies)	+	0	+	0	+
Aminoketone					
Bupropion*	+	0	0	+	+
Tetracyclins					
Mirtazapine	0	++	++	+	0
Tricyclics					
Amitriptyline	++++	+++	+++	+++	0
Clomipramine	++++	+++	++	+++	+
Desipramine	++	++	++	++	0
Nortriptyline	++	++	+	++	0

++++, high; +++, moderate; ++, low; +, very low; 0, absent. *Associated with higher risk of seizures, and lower risk of sexual dysfunction

¹adapted from: Dileo, JT et al Pharmacotherapy: A Pathophysiologic Approach 7th Edition, 2008; 1128 and Bezothinik-Bulter KZ et al. Clinical Handbook of Psychotropic Drugs 17th Edition, 2007; 81-83.

5. What happens to my client who is currently receiving escitalopram (Ciprallex®) paid by the WSIB whose claim comes up for renewal?

Payment for Ciprallex® may continue for workers who are receiving this drug benefit. New requests for Ciprallex® will not be approved. For claims whose Ciprallex® entitlement comes up for renewal, it is expected that professional judgment will be exercised to determine if the worker has benefited from the medication and merits continued use.

Formulary Drug Listing Decisions on Cipralex
Health Care Advice: Medications

WSIB RESTRICTED
 Please check with your manager before sharing this document externally.

Title: Frequently Asked Questions About Cymbalta

Abstract: This is a question and answer document about Cymbalta (Duloxetine).

Tags: Cymbalta; antidepressant; antidepressants for pain; treatment of pain; treatment of depression; cymbalta for back pain; frequently asked questions; health care advice; best practices for Cymbalta; WSIB Drug Formularies; Duloxetine; drug formulary; status update; medications; number needed to treat; NNT; opioids; TCA; Amitriptyline; Nortriptyline; Desipramine; Gabapentin; Pregabalin; Venlafaxine; Cymbalta renewal; payment of cymbalta

Last updated: 04/25/2013 11:21:07 AM **Contact:** [Tina Papastavros](#)

Author: [Tina Papastavros](#) **Feedback:** [Give us your feedback](#)

Questions and Answers - for internal use only

1. Doesn't duloxetine's dual mechanism of action present an advantage over other antidepressants or pain relieving agents that only have one mechanism of action?

Duloxetine exerts its effect by inhibiting the neuronal reuptake of two neurotransmitters, serotonin and epinephrine. This results in increased availability of the neurotransmitters to bind to postsynaptic receptors and ultimately results in an antidepressant and analgesic effect.

Although theoretically a dual mechanism of action should be advantageous, this has not necessarily been borne out in the results of randomized-controlled trials in depression. Studies comparing duloxetine to SSRIs (which only inhibit the reuptake of serotonin) have not demonstrated any advantage for duloxetine either in response and remission (absence of depressive symptoms) rates or in tolerability.

Unfortunately, duloxetine has never been compared directly to other analgesic for the treatment of neuropathic pain. Lacking comparative trials, we can try to assess the effectiveness of these agents by looking at the number needed to treat (NNT) associated with their use. The NNT below indicates the number of patients that must be given the drug in order for one person to experience at least a 50% reduction in pain (so, the lower the NNT the better the treatment, all other things being relatively equal):

Drug	NNT
TCA's (amitriptyline, nortriptyline, desipramine, etc.)	2.5
Gabapentin	4.0
Pregabalin	4.2
Venlafaxine	4.6

Duloxetine	5.2
Opioids	2.5 *

* considered last line due to potential for abuse and dependence

2. Are there any other antidepressants with a similar mechanism of action? How do they compare to duloxetine for the treatment of pain or depression?

Duloxetine is not unique in its dual mechanism of action. Venlafaxine, which has a similar dual mechanism of action, is another antidepressant with analgesic properties. Although they both inhibit serotonin and norepinephrine reuptake, trial results indicate that venlafaxine may actually be associated with better remission rates and tolerability. These two drugs have never been directly compared to each other for the treatment of neuropathic pain, however the NNT for one person to experience a 50% reduction in pain when taking venlafaxine is slightly lower than that for duloxetine. Venlafaxine costs significantly less than duloxetine.

3. Has duloxetine been proven effective in treating back pain?

No, duloxetine should generally not be prescribed to treat soft tissue / musculoskeletal back injuries. Most back injuries (excluding spinal cord injuries) are musculoskeletal in nature. Duloxetine has only been investigated in the treatment of chronic pain secondary to diabetic peripheral neuropathy or fibromyalgia. Duloxetine has never been proven effective in the treatment musculoskeletal pain.

4. What happens to my client who is currently receiving duloxetine paid by the WSIB and his claim comes up for renewal?

Payment for Duloxetine will continue for workers who were approved for entitlement prior to the effective date. Brand new requests for duloxetine will not be approved. For claims whose duloxetine entitlement comes up for renewal, it is expected that you will use your professional judgment to decide if the worker has benefited from the medication and merits continued use.

[Formulary Status Update on Cymbalta \(Duloxetine\)](#)
[Health Care Advice: Medications](#)

WSIB RESTRICTED
Please check with your manager before sharing this document externally.

Title: Frequently Asked Questions about Desvenlafaxine

Abstract: This is a question and answer document about Desvenlafaxine (Pristiq)

Tags: Pristiq; Effexor; Effexor XR; desvenlafaxine; antidepressant; desvenlafaxine to treat neuropathic pain; FAQ; frequently asked questions Pristiq; health care advice; anti depressant medication; antidepressant medication; best practices; WSIB Drug Formularies; Health Services Division; Venlafaxine; Duloxetine; icyclic antidepressants; TCAs; bupropion; desvenlafaxine renewal; Pristiq renewal.

Last updated: 04/25/2013 11:22:07 AM

Contact: [Tina Papastavros](#)

Author: [Sumeet Sidhu](#)

Feedback: [Give us your feedback](#)

Questions and Answers - for internal use only

1. Are there any other antidepressants with a similar mechanism of action? How do they compare to desvenlafaxine for the treatment of depression?

Desvenlafaxine is an active metabolite of the drug venlafaxine (Effexor XR®, generics). The two drugs appear to have similar pharmacology and safety profiles. Venlafaxine is considered to be the most relevant comparator to desvenlafaxine. However, desvenlafaxine and venlafaxine have never been directly compared to one another for any indication. Desvenlafaxine appears to cause more nausea than venlafaxine while venlafaxine appears to be associated with greater loss of appetite. Generic venlafaxine costs significantly less than desvenlafaxine, and is available on the appropriate WSIB formularies. Duloxetine is another serotonin and norepinephrine reuptake inhibitor (SNRI) with a similar mechanism of action. Duloxetine is not listed on WSIB formularies (see Drug Formulary Status Update – [Duloxetine](#)).

2. Are there specific criteria a worker must meet before payment for desvenlafaxine is considered?

No, there are no specific criteria for consideration of desvenlafaxine. Desvenlafaxine is not listed on any WSIB formulary and will not be reimbursed.

3. Which alternatives are available on WSIB formularies for the treatment of depression?

Medications available on WSIB formularies for the treatment of depression include venlafaxine, SSRIs (e.g., citalopram, sertraline, etc.), tricyclic antidepressants (TCAs), and bupropion.

Venlafaxine and SSRIs are recommended as first-line options according to North American guidelines. Evidence from randomized, controlled trials suggests that venlafaxine (Effexor®, generics) may lead to higher remission rates than SSRIs.

4. Can desvenlafaxine be used to treat neuropathic pain?

There are no published trials assessing the efficacy of desvenlafaxine in the treatment of pain of any type. Thus, desvenlafaxine should not be approved for the treatment of pain.

5. What alternatives do we currently have on our formularies for the treatment of chronic non-cancer pain (CNCP)?

Various alternative drug classes are currently available on the WSIB formularies. They include:

Nociceptive pain analgesics

- Acetaminophen
- NSAIDs (e.g., diclofenac, naproxen, ibuprofen, etc.)
- Cox-2 Inhibitors (celecoxib)
- Narcotics* (e.g., Tylenol 3®, codeine phosphate, Codeine Contin®).

Neuropathic pain analgesics

- Tricyclic antidepressants (desipramine, amitriptyline, nortriptyline, imipramine)
- Anticonvulsants (e.g., gabapentin)
- Serotonin Norepinephrine Reuptake Inhibitor (e.g., venlafaxine XR)
- Narcotics* (e.g., Tylenol 3®, codeine phosphate, Codeine Contin®).

* Due to the risk of adverse effects, including abuse and addiction, narcotics should be considered only after other treatments have failed to produce an adequate response. For new injuries and recurrences, the graduated narcotics management approach treatment may apply.

6. What happens to my client who is currently receiving duloxetine paid by the WSIB and his claim comes up for renewal?

Payment for desvenlafaxine will continue for workers who were approved for entitlement prior to the effective date. Brand new requests for desvenlafaxine will not be approved. For claims whose desvenlafaxine entitlement comes up for renewal, it is expected that you will use your professional judgment to decide if the worker has benefited from the medication and merits continued use.

[Formulary Status Update on Desvenlafaxine](#)
[Health Care Advice: Medications](#)

WSIB RESTRICTED
Please check with your manager before sharing this document externally.

Title: Frequently Asked Questions About Hydromorphone HCL (prolonged release)

Abstract: Frequently asked questions about Hydromorphone HCL (prolonged release), Journista.

Tags: Hydromorphone; Hydromorph HCL; Journista; Hydromorphone HCL; long acting opioid; long acting opioids; chronic opioid therapy; FAQ; Frequently Asked Questions; Journista entitlement; Journista renewal; hydromorphone HCL prolonged release; Health Care Advice; Medications; Narcotic strategy

Last updated: 04/25/2013 11:23:08 AM

Contact: [Tina Papastavros](#)

Author: [Tina Papastavros](#)

Feedback: [Give us your feedback](#)

Questions and Answers - for internal use only

1. How does hydromorphone HCL prolonged release (Journista®) compare with other long-acting opioids (e.g., Hydromorph Contin®) in terms of efficacy and safety?

Hydromorphone HCL prolonged release (PR) has never been directly compared to any other long-acting opioid formulation. There is no evidence that it is more effective or safer than other opioids or other formulations of hydromorphone.

2. What alternative opioids are available through the WSIB Drug Benefit Program?

There are numerous long-acting opioids available to workers who require chronic opioid therapy. These include a twice daily formulation of long-acting hydromorphone (Hydromorph Contin®).

3. Won't taking the medication once daily make things easier for workers on chronic opioid therapy?

There is no evidence that taking opioids once daily rather than twice daily improves compliance or quality of life. Most workers are able to take medications twice daily without any issues.

4. Hasn't hydromorphone HCL PR (Journista®) been shown to decrease the risk of abuse and dependence compared to other opioids?

Journista® employs an osmotic controlled release delivery system (OROS® technology) to deliver stable drug concentrations, uniform drug effects, and decreased dosing frequency. This delivery system renders Journista® tablets harder to crush and the hydromorphone more difficult to extract. It is

postulated that these properties make Jurnista® less likely to be abused or diverted. However, a review of data by the Controlled Substance Staff of the Food and Drug Administration (FDA) concluded that prolonged release hydromorphone (marketed as Exalgo® in the United States), continued to have a high risk of abuse potential despite the use of the OROS® technology. The review noted that:

- Hydromorphone has a higher abuse potential than many other opioids
- The extended release formulation contained much higher doses than immediate release formulation (hence, posing a higher risk of abuse and overdose)
- Biting provided enough force to crush the OROS® tablet, thereby circumventing the controlled release properties and resulting in immediate release characteristics (i.e., providing immediate drug effects).

FDA Center for Drug Evaluation and Research Memorandum

5. What happens to my client who is currently receiving Jurnista® paid by the WSIB whose claim comes up for renewal?

Payment for Jurnista® will continue for workers who were approved for entitlement prior to the effective date. Brand new requests for Jurnista® will not be approved. For claims whose Jurnista® entitlement comes up for renewal, it is expected that professional judgment will be exercised to determine if the worker has benefited from the medication and merits continued use. The Narcotic Strategy should be followed at all times.

Formulary Status Update for Hydromorphone HCL (prolonged release)

Health Care Advice: Medications

WSIB RESTRICTED
 Please check with your manager before sharing this document externally.

Title: Frequently Asked Questions About Hypnotics

Abstract: This is a question and answer document about Hypnotics: Zopiclone, Trazadone, Tryptophan.
 Tags: Zopiclone; Trazadone; Tryptophan; Insomnia medication; insomnia drug; treatment of insomnia; health care advice; medication; WSIB Drug Formularies; drug formulary; medications; side effects; benzodiazepine; benzodiazepines; BZD; SMR; skeletal muscle relaxant; hypnotic
 Last updated: 04/26/2013 11:20:53 AM Contact: [Tina Papastavros](#)
 Author: [Tina Papastavros](#) Feedback: [Give us your feedback](#)

Questions and Answers - for internal use only

1. In which formularies will zopiclone, trazadone, and tryptophan be available to injured workers?

Zopiclone is listed in the burn (05WS), cancer (19WS), tinnitus (20WS), psychotraumatic (22WS) and initial musculoskeletal (25WS) formularies only. Zopiclone is listed in the initial musculoskeletal formulary for the short-term treatment of insomnia associated with musculoskeletal injuries.

Trazadone is listed in the burn (05WS), cancer (19WS), tinnitus (20WS), psychotraumatic (22WS) and initial musculoskeletal (25WS) formularies only. Trazadone is listed in the initial musculoskeletal formulary for the short-term treatment of insomnia associated with musculoskeletal injuries.

Tryptophan is indicated as adjunctive treatment in bipolar affective disorder. It is listed in the psychotraumatic formulary (22WS) only. There is no rigorous evidence for the use of tryptophan in insomnia; therefore, tryptophan is not listed as a hypnotic on any other formularies.

2. Why is trazadone as a hypnotic being approved for short-term use only (excluding burn, tinnitus and cancer)? Since it has a lower risk of abuse and dependence compared to zopiclone and benzodiazepines, can't it be used for the long-term treatment of insomnia?

Overall, there is insufficient evidence available to determine the optimal duration of hypnotic therapy. Although trazadone has a lower risk of dependence than zopiclone, its safety and efficacy for long-term use in patients with sleep disturbances requires further study. Thus, as a hypnotic it is being placed in the short-term initial musculoskeletal formulary for workers with a musculoskeletal injury.

3. What are the potential risks of long-term zopiclone use?

Long-term use of zopiclone can result in physical or psychological dependence, particularly with the use of higher doses. There have been several reports of zopiclone abuse in patients who developed

tolerance to the drug.

4. What happens when zopiclone is discontinued abruptly?

Zopiclone should not be discontinued abruptly. Withdrawal reactions similar to those of benzodiazepines have been reported. Symptoms include insomnia, agitation, headache, myalgias, myoclonus, tremor, loss of appetite, GI distress, perceptual disturbances, and seizures. More severe reactions have been reported in patients suddenly discontinuing zopiclone after taking high doses for prolonged periods of time. Gradual tapering of zopiclone is recommended in individuals who have taken the medication for more than a few weeks (especially in individuals with a history of seizure disorders).

5. What happens to my client who is currently receiving zopiclone, trazodone, or tryptophan as a hypnotic paid by the WSIB whose claim comes up for renewal?

Payment for zopiclone, trazodone, and tryptophan will continue for workers who were approved for entitlement prior to the effective date. Brand new requests for zopiclone or trazodone outside 25WS, 22WS, 20WS, 19WS, and 05WS formularies will not be approved. Brand new requests for tryptophan as a hypnotic will not be approved. For claims whose zopiclone, trazodone, or tryptophan entitlement comes up for renewal, it is expected that professional judgment will be exercised to determine if the worker has benefited from the medication and merits continued use.

Hypnotics

Health Care Advice: Medications

WSIB RESTRICTED
Please check with your manager before sharing this document externally.

File: Frequently Asked Questions About Benzodiazepines

Abstract: This is a question and answer document about Benzodiazepines.

Tags: benzodiazepine; benzodiazepines; chlordiazepoxide; clorazepate; diazepam; flurazepam; alprazolam; bromazepam; clobazam; clonazepam; lorazepam; nitrazepam; oxazepam; lamazepam; triazolam; medications best practices; WSIB Drug Formularies; drug formulary; status update; medications; indication; BZD; SMR; skeletal muscle relaxant; hypnotic; health care advice; risks; side effects; long term use; used with narcotics; benzodiazepine renewal.

Last updated: 04/25/2013 11:13:19 AM Contact: [Tina Papastavros](#)
Author: [Tina Papastavros](#) Feedback: [Give us your feedback](#)

Questions and Answers - for internal use only

1. Why aren't benzodiazepines listed in the 025WS formulary? What drugs are available in the Initial musculoskeletal formulary (25WS) for the short-term treatment of sleep disturbances or muscle spasm/spasticity?

The use of benzodiazepines (BZDs) for the treatment of musculoskeletal conditions and insomnia is not recommended due to concerns regarding lack of evidence for efficacy (as skeletal muscle relaxants) or safety (as hypnotics and skeletal muscle relaxants). Zopiclone and trazodone will be listed in the 25WS formulary for short-term use as hypnotics. Systematic reviews have concluded that these agents may pose a lower risk of psychomotor impairment or abuse and dependence. Cyclobenzaprine and orphenadrine will be listed in the 25WS formulary for the short-term treatment of muscle spasm. Notably, safety concerns exist regarding the long-term use of any hypnotic or skeletal muscle relaxant (SMR); hence, these agents will not be added to any other formularies for the treatment of these indications.

Side effects are also usually dependent on dose prescribed and pharmacokinetic characteristics. Benzodiazepines with long half-lives may cause daytime drowsiness and cognitive impairment when prescribed in higher doses.

2. What are the differences between the benzodiazepines prescribed for injured workers assigned to formularies 03WS, 05WS, 19WS, 20WS, and 22 WS?

Benzodiazepines are listed in these formularies for use other than as hypnotics or SMRs.

Benzodiazepines all have similar pharmacological profiles. The effects of each drug will depend on the dose prescribed and its pharmacokinetic properties. Pharmacokinetic properties of BZDs available in Canada are listed below. Benzodiazepines (and their active metabolites) with a long half-life that accumulate in the body's lipid stores can result in prolonged effects. Generally, long-acting agents may be prescribed for conditions that require continued drug effects (e.g., anxiety disorders, seizures).

Most BZDs are metabolized via hepatic oxidation and demethylation. Those that undergo conjugation (and do not have an active metabolite) are less likely to accumulate and are preferred in older individuals and those with reduced hepatic function.

Benzodiazepine	Approximate Equivalent Dose (mg)	Onset of action (hrs)	Metabolic Pathway	Active Metabolite	Half-life (hrs) [parent and active metabolite]
Long-acting					
Chlordiazepoxide	10	1-3	Oxidation	Yes	100
Clorazepate	7.5	1	Oxidation	Yes	100
Diazepam	5	1	Oxidation	Yes	100
Flurazepam	15	1	Oxidation	Yes	100
Alprazolam	0.5	1-3	Oxidation	Yes	12-15
Intermediate-acting					
Bromazepam	3	1-3	Conjugation	Yes	8-30
Clobazam	10	1-3	Oxidation	Yes	10-46
Clonazepam	0.25	1-3	Oxidation	No	20-80
Lorazepam	1	1-3	Conjugation	No	10-20
Nitrazepam	5	1-3	Reduction	No	16-55
Oxazepam	15	> 3	Conjugation	No	5-15
Temazepam	15	1-3	Conjugation	No	10-20
Short-acting					
Triazolam	0.25	< 1	Oxidation	No	1.5-5

Modified from the Canadian Compendium of Pharmaceutical Specialties 2009

3. What are the potential risks of long-term benzodiazepines use?

There is a risk of developing psychological and physical dependence with long-term use of benzodiazepines at therapeutic doses. This may also occur with short-term use, especially with high doses. Tolerance to the hypnotic effects usually develops within one month of continuous use.

Rebound insomnia can occur after abrupt discontinuation of a benzodiazepine. The lowest dose, for

the shortest duration possible should be prescribed to minimize this and other adverse events.

4. How can the risk of dependence be reduced?

The risk of psychological or physical dependence on benzodiazepines can be reduced by carefully titrating the dose, close observation and follow up, screening for risk factors prior to use, and providing appropriate patient education. In general, benzodiazepines should be avoided in patients with a history of alcohol or substance abuse.

5. What happens when benzodiazepines are discontinued abruptly? Are there any references available for tapering the use of benzodiazepines?

Individuals abruptly discontinuing benzodiazepines may experience withdrawal reactions within 1-2 days (short-acting) to 5-10 days (long-acting). Symptoms include insomnia, agitation, headache, myalgias, myoclonus, tremor, loss of appetite and GI distress. Serious withdrawal reactions include seizures, coma, and psychotic states. As such, benzodiazepine tapering should be done slowly and under the supervision of a physician.

Several references are available to provide guidance on tapering benzodiazepines and include the recently published Canadian Guideline for Safe and Effective Use of Opioids for CNCP-Part B (available at: <http://nationalpaincentre.mcmaster.ca/opioid/>).

6. Can benzodiazepines be used concurrently with narcotics?

Benzodiazepines and narcotics can interact to produce additive central nervous system effects. The concurrent use of benzodiazepines and narcotics has been linked to an increased risk of sedation, overdose, and impaired functioning.

Concurrent use of narcotics and benzodiazepines can also contribute to oxygen desaturation; cautious use is warranted in individuals with sleep apnea.

7. What happens to my client who is currently receiving a benzodiazepine paid by the WSIB and his claim comes up for renewal?

Payment for benzodiazepines will continue for workers who were approved for entitlement prior to the effective date. Brand new requests for benzodiazepines outside the formularies in which they are listed will not be approved. For claims whose benzodiazepine entitlement comes up for renewal, it is expected that professional judgment will be exercised to determine if the worker has benefited from the medication and merits continued use.

[Benzodiazepines](#)

[Health Care Advice: Medications](#)


Title: Frequently Asked Questions About Lyrica

Abstract: This is a question and answer document about Lyrica.

Tags: Lyrica; pregabalin; gabapentin; GABA; venlafaxine; opioids; side effects; medication treatment for neuropathic pain; neuropathic pain; drugs for neuropathic pain; neuro pain; treatment of neuro pain; health care advice; medication; fibromyalgia pain; treatment of fibromyalgia pain; medication for fibromyalgia; best practices; WSIB Drug Formularies; Health Services Division; drug formulary; status update; medications; indication; TCA; Gabapentin; number needed to treat; NNT; anticonvulsants; amitriptyline; nortriptyline; desipramine; neuropathic pain analgesics; pregabalin for back injuries; treatment of chronic pain; Lyrica renewal; lyrica review

Last updated: 04/26/2013 10:04:26 AM

Contact: [Tina Papastavros](#)

Author: [Tina Papastavros](#)

Feedback: [Give us your feedback](#)

Questions and Answers - for internal use only

1. How does pregabalin compare to gabapentin?

Gabapentin and pregabalin are both anticonvulsants with analgesic properties and are very similar in structure and pharmacology. Both being derived from an inhibitory neurotransmitter called α -aminobutyric acid (GABA). Gabapentin and pregabalin exert their analgesic effects by acting on the calcium channel ions in the CNS to decrease the transmission of pain neurotransmitters and to modulate pain signals.

Gabapentin is usually taken in three divided doses. The most common adverse effects reported with its use include drowsiness, dizziness, diplopia, ataxia and headaches. Pregabalin can be taken either twice or three times daily. The most commonly reported adverse events with pregabalin treatment also include drowsiness and dizziness. Additionally, peripheral edema and weight gain have also been reported.

Gabapentin and pregabalin have never been compared to each other in a randomized, controlled trial. Most systematic reviews of trials in neuropathic pain and evidence-based guidelines have concluded that these medications have a similar effect in pain reduction. Overall, the evidence indicates that pregabalin does not offer any clinical or cost advantage to gabapentin.

2. How effective in treating neuropathic pain are the alternative pain relieving agents listed on the WSIB formularies?

Various classes of medications have demonstrated efficacy in treating neuropathic pain. Most of these medications have not been compared in head-to-head trials. Lacking comparative trials, we can try to assess effectiveness of these agents by looking at the number needed to treat (NNT) associated with their use.

For neuropathic pain, the NNT below indicates the number of patients that must be given the drug in order for one person to experience at least a 50% reduction in pain (so, the lower the NNT the better the treatment, all other things being relatively equal):

Drug	NNT
TCA's (amitriptyline, nortriptyline, desipramine, etc.)	2.5
Gabapentin	4.0
Pregabalin	4.2
Venlafaxine	4.6
Opioids	2.5 *

* considered last line due to potential for abuse and dependence

3. What are the alternatives listed on WSIB formularies for treating patients who are diagnosed with fibromyalgia pain?

American and European guidelines have reviewed the evidence in the treatment of fibromyalgia. The following agents are listed on WSIB formularies and have been recommended as effective by both guidelines:

- TCAs
- Selective Serotonin Reuptake inhibitors (e.g, fluoxetine)
- Weak opioids (last-line).

4. Can pregabalin be used to treat back injuries?

No, pregabalin should not be used to treat most back injuries. The majority of back injuries (excluding spinal cord injuries) are musculoskeletal in nature. Pregabalin has only been investigated in chronic pain secondary to neuropathy or fibromyalgia. Pregabalin has never been proven effective in the treatment musculoskeletal pain.

5. If a request is made to review a long-standing case on the merits and justice of pregabalin treatment, what should I consider in trying to determine if I should authorize its extraordinary use?

Requests for pregabalin entitlement for claims without an established history of prior drug treatment will not be approved. In cases where a request is made to review the file in order to determine whether authorization of extraordinary use is merited, you should only approve the request for claims in which you can document in the file all three of the following specific criteria:

- (i) neuropathic pain as a diagnosis;

- (ii) previous trials of two TCAs and gabapentin; and
- (iii) adequate duration (at least two months) or the emergence of intolerable side effect(s) for the previous drug trials.

If you cannot document all three of the above-mentioned criteria, the request for extraordinary use should not be approved.

6. Can authorization for extraordinary use of pregabalin be granted for a worker who has recently been diagnosed with neuropathic pain and has only had one short trial of an alternative agent?

No, workers who do not meet the specific criteria outlined above (Q.5) should not be approved. Workers with a diagnosis of neuropathic pain due to a work-related injury who do not meet the specific criteria outlined above are entitled to reimbursement for the following agents with proven efficacy in treating neuropathic pain:

Neuropathic pain analgesics

- Tricyclic antidepressants (desipramine, amitriptyline, nortriptyline, imipramine)
 - Anticonvulsants (e.g., gabapentin)
 - Serotonin Norepinephrine Reuptake Inhibitor (venlafaxine XR)
 - Opioids (e.g., Tylenol 3®, codeine phosphate, Codeine Contin®).
-

7. Can pregabalin and gabapentin be used at the same time?

Pregabalin and gabapentin are extremely similar in structure and pharmacology. There is no reason to believe or evidence to support the idea that combining these medications would increase their effectiveness.

8. What happens to my client who is currently receiving pregabalin paid by the WSIB and his claim comes up for renewal?

Payment for pregabalin will continue for workers who were approved for entitlement prior to the effective date. Brand new requests for pregabalin will not be approved. For claims whose pregabalin entitlement comes up for renewal, it is expected that you will use your professional judgment to decide if the worker has benefited from the medication and merits continued use.

[Formulary Drug Listing Decisions on Lyrica \(Pregalin\)](#)
[Health Care Advice: Medications](#)

WSIB RESTRICTED
Please check with your manager before sharing this document externally.

Title: Frequently Asked Questions About Oxycodone (Controlled Release 5mg Tablets)

Abstract: This is a question and answer document about Oxycodone (Controlled Release 5mg Tablets).
Tags: Oxycodone; Controlled Release; Oxycontin 5 mg tablets; Oxycontin; FAQ; oxycodone questions and answers; pms-oxycodone; endocet; Drug Benefits Program; health care advice; medication; drug; best practices; WSIB Drug Formularies; Health Services Division; payment of oxycontin 5mg; oxycontin 5mg renewal; oxycontin 5mg approval
Last updated: 04/26/2013 10:06:11 AM **Contact:** [Tina Papastavros](#)
Author: [Tina Papastavros](#) **Feedback:** [Give us your feedback](#)

Questions and Answers - for internal use only

1. Why is OxyContin® 5mg being removed from formularies when other strengths are available?

OxyContin® 5mg tablets are being removed from formularies because they do not provide any therapeutic benefit compared with similar low-dose short acting opioids or value for money. The need for such a small dose of oxycodone in a controlled-release formulation is unclear. Furthermore, OxyContin® 5mg tablets are more expensive on a per mg basis than any other strength of OxyContin®.

2. What alternatives are available to ill / injured workers?

Ill / injured workers who meet criteria for treatment with opioids will still have access to a wide variety of opioids in various formulations and strengths. Specifically, immediate-release oxycodone 5mg tablets (e.g., pms-oxycodone) and immediate release oxycodone-acetaminophen combination products (e.g, Endocet®) will still be listed on WISB formularies.

3. What happens to my client who is currently receiving OxyContin® 5mg tablets paid by the WSIB whose claim comes up for renewal?

Payment for OxyContin® 5mg will continue for workers who were approved for entitlement prior to the effective date. Brand new requests for OxyContin® 5mg will not be approved. For claims whose OxyContin® 5mg entitlement comes up for renewal, it is expected that professional judgment will be exercised to determine if the worker has benefited from the medication and

merits continued use.

[Formulary Drug Listing Decisions on Oxycodone \(Controlled Release 5mg Tablets\)](#)

[Health Care Advice: Medications](#)

[WSIB Drug Formularies](#)

WSIB RESTRICTED
Please check with your manager before sharing this document externally.

File: Frequently Asked Questions About Paliperidone and Ziprasidone

Abstract: This is a question and answer document about Paliperidone and Ziprasidone.

Tags: Ziprasidone; Paliperidone; antipsychotic medication; antipsychotics; antipsychotic drugs; risperidone; side effects; alternative antipsychotics in WSIB formulary; frequently asked questions; FAQ; adverse effects; Ziprasidone and treatment of pain; paliperidone and treatment of pain; sleep disorders treatment; PTSD meds; PTSD medications; PTSD drugs; WSIB health care advice medication; WSIB Drug Formularies; paliperidone renewal; paliperidone approval; ziprasidone renewal; ziprasidone approval; drug formulary; drug formulary updates.

Last updated: 04/26/2013 10:07:36 AM

Contact: [Tina Papastavros](#)

Author: [Tina Papastavros](#)

Feedback: [Give us your feedback](#)

Questions and Answers - for internal use only

1. How does ziprasidone compare to other second generation antipsychotics (SGA) listed on WSIB formularies?

Ziprasidone is a second generation antipsychotic which exerts its antipsychotic effects through the inhibition of dopamine-2 (D2) and serotonin 5-HT2A receptors in the brain. This is a similar mechanism of action to other SGAs currently list on WSIB formularies (e.g., olanzapine, risperidone, and quetiapine). However, despite having a similar mechanism of action to olanzapine and risperidone, ziprasidone was reported to be less effective in reducing the severity of psychotic symptoms in schizophrenia according to a meta-analysis of randomized controlled trials.

Olanzapine and ziprasidone are both associated with short-term weight gain. Long-term changes in weight are believed to contribute to olanzapine's increased risk of metabolic syndrome. Although a short-term trial revealed a lower risk of weight gain with ziprasidone, long-term data is not available. Hence, the long-term risk of ziprasidone-induced metabolic syndrome is unclear.

Ziprasidone causes dose-related prolongation of the QT-interval and has been associated with utricularial skin reactions. The risk for these serious reactions appears to be greater for ziprasidone compared to other SGAs.

Overall, there is no evidence to indicate that ziprasidone is associated with any clinically significant benefit in efficacy, safety, or cost compared to SGAs currently listed on WSIB formularies.

2. How does paliperidone compare to risperidone?

Risperidone is a SGA. When taken orally, it is broken down by the liver via cytochrome P450 D26 into its active metabolite paliperidone (which is primarily responsible for its antipsychotic effect). Since paliperidone is the active ingredient in both medications, they both exert their antipsychotic effects via the same mechanism (blockade of 5-HT2A and dopamine-2 receptors).

The most commonly reported adverse effects are similar for both medications and include headache, tachycardia, hypotension, somnolence, anxiety, and movement disorders. Weight gain and extrapyramidal symptoms (EPS) occur more frequently with increasing doses with both medications.

Paliperidone is available in a slow release preparation and is usually taken once daily. Due to paliperidone's OROS-osmotic slow release technology, tablets cannot be chewed or crushed. Risperidone is usually taken twice daily.

Paliperidone has never been compared directly to risperidone in a randomized, controlled trial; however, the medications appear to have similar effects in reducing psychotic symptoms. Overall, there is no evidence to indicate that paliperidone is associated with any clinically significant benefit in efficacy, safety, or cost compared to risperidone.

3. Can paliperidone and risperidone be used together?

Risperidone is broken down to the active metabolite, paliperidone, in the body (i.e., the active ingredient is the same in both medications). There is no reason to believe or evidence to support the idea that combining these medications would have any clinical benefit. Combining these two medications would lead to increased paliperidone levels and put individuals at greater risk of experiencing potentially serious adverse effects.

4. What alternative antipsychotics are listed on WSIB formularies and how do they compare in efficacy and side effects?

Various antipsychotic medications are available on the psychotraumatic formulary. They can be divided broadly into two groups – first-generation antipsychotics (sometimes referred to as “typical” antipsychotics) and second-generation antipsychotics (sometimes referred to as “atypical” antipsychotics). Examples of first generation antipsychotics (FGA) listed on formulary include haloperidol, perphenazine, loxapine, and chlorpromazine. Examples of SGAs listed on formulary include risperidone, olanzapine, and quetiapine.

Clinically, both groups of antipsychotics are effective in reducing psychotic symptoms. A recent critical overview of antipsychotic evidence suggested that FGAs and SGAs may not differ significantly in overall efficacy or safety. FGAs are associated with higher rates of extrapyramidal side effects compared to certain SGAs. The SGAs differ from each other considerably in pharmacology and in side effect profiles. A summary of the efficacy and side effects of FGAs and SGAs can be found in table 1 below.

Table 1: Comparison of First- and Second Generation Antipsychotic Efficacy and Side Effects¹

--	--	--	--	--	--	--	--	--	--

	Olanzapine	Quetiapine	Risperidone	Haloperidol	Perphenazine	Chlorpromazine
Efficacy						
positive symptoms	+++	++	+++	+++	+++	+++
negative symptoms	+	+	+	+	+	+
relapse (1 yr)	+++	?	+++	++	++	++
Adverse Effects						
anticholinergic	+	0	0	0	++	+++
cardiac repolarization	0	0	0	0	0	++
hypotension	++	++	+++	+	++	+++
hyperprolactinemia	+	0	++	++	++	++
Type 2 diabetes	++	+	+	+	+	+
sexual dysfunction	++	+	++	++	++	+++
weight gain	+++	++	+	0	+	++
EPS	+	0	++	++++	+++	++
NMS	+	+	+	+++	++	+

++++ = very high +++ = high ++ = moderate += low 0 = negligible ? = poorly defined

NMS = neuroleptic malignant syndrome EPS = extrapyramidal syndrome

1 adapted from Gardner, DM et al. CMAJ 2005; 172:1703-11

5. Can paliperidone or ziprasidone be approved for the treatment of pain?

Paliperidone and ziprasidone should not be approved for the treatment of pain in injured / ill workers. There are no randomized, controlled trials demonstrating efficacy for either of these medications in improving pain or function.

6. Can paliperidone or ziprasidone be approved for the treatment of sleep disorders?

Paliperidone and ziprasidone should not be approved for the treatment of sleep disorders in injured / ill workers. There are no randomized, controlled trials demonstrating efficacy; furthermore, the risk of adverse events with these medications (e.g., movement disorders, QT prolongation, urticaria, etc.) outweighs any unproven benefits in sleep disorders.

7. What are the treatment options available for workers diagnosed with a sleep disorder or PTSD due to a work-related injury?

Various guidelines have been published reviewing the evidence in the treatment of insomnia^{1, 2}. The following agents are listed on WSIB formularies and have been recommended as effective:

- First-line: zopiclone, temazepam
- Second-line: amitriptyline, trazodone, doxepine
- Third-line: L-tryptophan

1 Guideline for Adult Insomnia

(see http://www.topalbertadoctors.org/informed_practice/clinical_practice_guidelines/complete%20set/Insomnia/adult_insomnia_pda.pdf)

2 Schutte-Rodin, S et al. Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med 2008; 487-504.

The Canadian Psychiatric Association has reviewed the evidence in the treatment of PTSD. The following agents are listed on WSIB formularies and have been recommended as effective³ (list not all inclusive):

- First line: fluoxetine, paroxetine, sertraline, venlafaxine XR
- Second-line: fluvoxamine, mirtazapine, moclobemide, phenelzine
- Adjunctive agents: risperidone, olanzapine
- Third-line: amitriptyline, imipramine
- Adjunctive agents: carbamazepine, gabapentin, lamotrigine, valproate, bupropion, citalopram, quetiapine, buspirone.

3 Canadian Psychiatric Association. Clinical practice guidelines. Management of anxiety disorders. Can J Psychiatry. 2006;51(8Suppl2):9S-91S.

8. What happens to a worker who is currently receiving paliperidone or ziprasidone paid by the WSIB and the claim comes up for renewal?

Payment for paliperidone and ziprasidone will continue for workers who were approved for entitlement prior to the effective date. Brand new requests for paliperidone or ziprasidone will not be approved. For claims whose paliperidone or ziprasidone entitlement comes up for renewal, it is expected that you will use your professional judgment to decide if the worker has benefited from the medication and merits continued use.

[Formulary Status Update on Paliperidone](#)

[Formulary Status Update on Ziprasidone](#)

[Health Care Advice: Medications](#)

WSIB RESTRICTED
Please check with your manager before sharing this document externally.

Title: **Frequently Asked Questions About Pennsaid**

Abstract: This is a question and answer document about Pennsaid.

Tags: Pennsaid; treatment of neuropathic pain; neuro pain; neuropathic pain; treatment of osteoarthritis; osteoarthritis; OA; oa; side effects; indications; adverse effects; GI complications; pennsaid and GI safety; approval of Pennsaid; allowance of Pennsaid; renewal of Pennsaid; health care advice; medication; drug; best practices; WSIB Drug Formularies; oral diclofenac; Health Services Division; inflammation; oral NSAIDs; ulcers; COX-2 Inhibitor; musculoskeletal pain; soft tissue injury; gastrointestinal complications; Compus / RxFiles

Last updated: 04/26/2013 10:08:53 AM Contact: [Tina Papastavros](#)
 Author: [Tina Papastavros](#) Feedback: [Give us your feedback](#)

Questions and Answers - for internal use only

1. Is Pennsaid® effective in treating neuropathic pain or other joints affected by osteoarthritis (OA) (i.e., joints other than the knee)?

Pennsaid® has only been investigated in the treatment of primary OA of the knee. It should only be prescribed to treat pain and inflammation of a local / superficial joint (e.g., knee or hand). Pennsaid® has never been investigated in and should not be authorized for any of the following conditions:

- neuropathic pain
- general musculoskeletal pain / soft tissue injury (e.g., back injuries)
- osteoarthritis of large, deep joints (e.g., hip, spine, etc.).

Guidelines for the treatment of neuropathic pain and for the treatment of OA of the hip do not recommend the use of Pennsaid®.

2. How do the side effects of Pennsaid® compare to oral NSAIDs?

In the one trial that compared Pennsaid® to oral diclofenac, the most commonly reported adverse events were dry skin at the application site (Pennsaid®) and dyspepsia (oral diclofenac). Interestingly, overall more patients discontinued Pennsaid® treatment than oral diclofenac in this trial (indicating that the latter may be easier to tolerate).

Short-term Pennsaid® use may be associated with a lower risk of harm in individuals at high-risk of NSAID-induced ulcers. However, the gastrointestinal (GI) safety of Pennsaid® beyond 12 weeks is unclear and the manufacturer's monograph does not recommend its use (intermittent or continuous) beyond 3 months.

3. What treatment options are recommended and available for a worker with OA of a local joint

who is at high-risk of GI complications?

Risk factors* for NSAID-induced ulcers comprise:

- age > 60 years
- a history of ulcers or upper GI bleed
- concurrent warfarin or steroid treatment
- concurrent or high dose NSAID therapy (i.e., greater twice the regular dose)
- co-morbid chronic illness (e.g., heart disease).

Individuals with multiple risk factors are at highest risk. For those at high-risk, treatment options* include:

- avoidance of NSAIDs / use of acetaminophen (for mild-moderate pain)
- use of lowest possible NSAID dose for the shortest duration
- GI ulcer prophylaxis with standard dose proton pump inhibitor (e.g., generic omeprazole) or misoprostol.

(Note: all proton pump inhibitors have similar efficacy in preventing NSAID-induced ulcers)

*See [Compus / RxFiles](#): Gastrointestinal-acid suppression drugs: evidence, tips, and pearls; available online at and Canadian Agency for Drugs and Technologies in Health. Evidence for PPI use in gastroesophageal reflux disease, dyspepsia and peptic ulcer disease [Scientific report]. Ottawa: The Agency; 2007.

4. If a request is made to review a case on the merits and justice of Pennsaid® treatment, what should I consider in trying to determine if I should authorize its extraordinary use?

Request for Pennsaid® entitlement for claims where pain is secondary to a musculoskeletal / soft tissue injury, neuropathy, or osteoarthritis of a large deep joint (e.g., hip or spine) will not be approved. In cases where a request is made to review the file in order to determine whether authorization for extraordinary use is merited, the request should only be approved for claims in which all three of the following specific criteria can be documented in the file:

- (i) use will be strictly limited to a local / superficial joint [e.g., knee, wrist, elbow, etc.];
- (ii) use will be limited to 12 weeks; and
- (iii) an NSAID / COX-2 inhibitor will not be used concurrently.

Furthermore, in cases where a worker is not a high risk for GI adverse events, the worker must have tried and failed a sufficient trial of an oral NSAID. If all three of the abovementioned criteria cannot be documented, the request for extraordinary use should not be approved.

5. Should Pennsaid® be taken along with another oral NSAID?

Pennsaid® should not be used with an oral NSAIDs or high dose ASA due to the risk of additive adverse events (e.g., gastritis). Low-dose ASA (325mg) is acceptable, however.

6. What happens to a worker who is currently receiving Pennsaid® paid by the WSIB and the claim comes up for renewal?

Payment for Pennsaid® will continue for workers who were approved for entitlement prior to the effective date. Brand new requests for Pennsaid® will not be approved. For claims whose Pennsaid® entitlement comes up for renewal, it is expected that you will use your professional judgment to decide if the worker has benefited from the medication and merits continued use.

Formulary Status Update on Pennsaid
Health Care Advice: Medications

WSIB RESTRICTED
Please check with your manager before sharing this document externally.

Title: **Frequently Asked Questions About Piroxicam**

Abstract: This is a question and answer document about Piroxicam.

Tags: Piroxicam; NSAIDs; FAQ; frequently asked questions; GI complications; oral NSAIDs; NSAID therapy; chronic pain; risk factors Piroxicam; alternative NSAIDs; NSAID induced ulcer treatment; inflammation; Drug Benefits Program; risk factors NSAIDs; Ibuprofen; health care advice; medication; drug; best practices; WSIB Drug Formularies; Health Services Division; Health Canada Advisory; Campus/RxFiles

Last updated: 04/26/2013 10:09:55 AM

Contact: [Tina Papastavros](#)

Author: [Tina Papastavros](#)

Feedback: [Give us your feedback](#)

Questions and Answers - for internal use only

1. I have an injured worker who has been receiving piroxicam for over 6 months. Should he be switched to another NSAID?

No, the injured worker can remain on the piroxicam as he is using it for chronic pain and/or inflammation. The increased risk for the development of the serious skin reactions is most important during the first 8 weeks of treatment. For the GI complications, conflicting results have been reported on the relationship of the risk of GI events and the length of time the patient is on the NSAID, although some studies indicate that the risk is highest in the first month of NSAID use.

2. An injured worker takes piroxicam only occasionally to treat flares of pain and inflammation. Does the long-term but occasional use of piroxicam put the worker at high or low risk of these adverse events?

Intermittent use of piroxicam to treat "flares" (e.g., used once a month) should be considered as "new" treatment when taken again. The injured worker should discuss the risks vs. benefits of piroxicam treatment with their physician. The WSIB will fund an alternative NSAID available through the Drug Benefits Program.

3. Where can I find more information about the Health Canada advisory and literature about the risks associated with acute, short-term piroxicam use?

The Health Canada Advisory can be located online at [Health Canada](#). More information regarding the serious skin reactions and GI toxicity with piroxicam use can be found in the following references:

(i) Laporte JR, Ibanez L, Vidal X, et al. Upper gastrointestinal bleeding associated with the use of NSAIDs : newer versus older agents. *Drug Saf* 2004;27:411-20.

(ii) Hernandez-Diaz S, Rodriguez LA. Association between nonsteroidal antiinflammatory drugs and upper gastrointestinal tract bleeding/perforation : an overview of epidemiologic studies published in the

1990s. Arch Intern Med 2000;160:2093-9.

(iii) Garcia Rodriguez LA, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual nonsteroidal antiinflammatory drugs. Lancet 1994;343:769-72.

(iv) Henry D, Lim LL, Garcia Rodriguez LA, et al. Variability in risk of gastrointestinal complications with individual nonsteroidal anti-inflammatory drugs : results of a collaborate meta-analysis. BMJ 1996;312:1563-6.

(v) Richy F, Bruyere O, Ethgen O, et al. Time dependent risk of gastrointestinal complications induced by non-steroidal anti-inflammatory drug use: a consensus statement using a meta-analytic approach. Ann Rheum Dis 2004;63:759-66.

(vi) Richy F, Scarpignato C, Lanus A, Reginster JY. Efficacy and safety of proxicam revisited. A global meta-analysis of randomized clinical trials. Pharmacol Res 2009;60:254-63.

(vii) Bigby M, Stern R. Cutaneous reactions to nonsteroidal anti-inflammatory drugs. A review. J Am Acad Dermatol 1985;12(5 pt 1):866-76.

(viii) Mockenhaupt M, Kelly JP, Kaufman D, et al. The risk of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with nonsteroidal antiinflammatory drugs: a multinational perspective. J Rheumatol 2003;30:2234-40.

4. What alternative NSAIDs are available on WSIB formularies for treating injured workers suffering from acute pain or inflammation?

Various NSAIDs are available on WSIB formularies that are associated with a lower risk of serious skin reactions and GI toxicity. They include:

- Ibuprofen
- Indomethacin
- Diclofenac
- Naproxen
- Ketoprofen
- Sulindac
- Celecoxib (selective COX-II inhibitor).

5. What are the risk factors for NSAID-induced ulcer and what options exist for prevention?

Risk factors* for NSAID-induced ulcers include:

- age > 60 years
- a history of ulcers or upper GI bleed
- concurrent warfarin or corticosteroid treatment (e.g., prednisone)
- concurrent or high dose NSAID therapy (i.e., greater twice the regular dose)
- co-morbid chronic illness (e.g., heart disease)

Individuals with multiple risk factors are at highest risk. For those at high-risk, treatment options*

include:

- avoidance of NSAIDs and use of acetaminophen (for mild-moderate pain)
- use of lowest possible NSAID dose for the shortest duration
- GI ulcer prophylaxis with standard dose proton pump inhibitor (e.g., generic omeprazole) OR misoprostol

(Note: all proton pump inhibitors have similar efficacy in preventing NSAID-induced ulcers)

*See [Compus/RxFiles](#) (Gastrointestinal-acid suppression drugs: evidence, tips, and pearls) and Canadian Agency for Drugs and Technologies in Health. Evidence for PPI use in gastroesophageal reflux disease, dyspepsia and peptic ulcer disease [Scientific report]. Ottawa: The Agency; 2007.

Formulary Status Update on Piroxicam

Health Care Advice: Medications updated

WSIB RESTRICTED
Please check with your manager before sharing this document externally.

Title: Frequently Asked Questions About Skeletal Muscle Relaxants

Abstract: This is a question and answer document about Skeletal Muscle Relaxants.

Tags: Muscle Relaxant; muscle relaxants; cyclobenzaprine; orphenadrine; SMR; NSAIDs; nonsteroidal anti-inflammatory drugs; health care advice; tizanidine; medications acute low back pain; acute low back pain medication; drug; best practices; WSIB Drug Formularies; drug formulary; status update; medications; Indication; a benzodiazepine; benzodiazepines; BZD; SMR; skeletal muscle relaxant; hypnotic; payment of baclofen; tizanidine; orphenadrine; cyclobenzaprine; skeletal muscle relaxants renewal; skeletal muscle relaxants approval.

Last updated: 04/26/2013 10:11:03 AM

Contact: [Tina Papastavros](#)

Author: [Tina Papastavros](#)

Feedback: [Give us your feedback](#)

Questions and Answers - for internal use only

1. Can cyclobenzaprine and orphenadrine be approved for long-term use?

No, there are no long-term trials investigating the efficacy or safety of these drugs. Concerns regarding side effects should limit their use to short-term treatment (i.e., ≤ 3 weeks) of acute low back and neck pain / spasm.

2. It seems as if benzodiazepines are often prescribed as SMRs, why aren't they also included in the initial musculoskeletal formulary? Aren't they effective skeletal muscle relaxants?

There is limited evidence for the use of benzodiazepines as skeletal muscle relaxants (SMRs). Systematic reviews of trials in which benzodiazepines were prescribed as SMRs in the treatment of spinal cord injuries, mechanical neck injuries, and neurological diseases were of poor quality and revealed marginal to no benefit. Systematic reviews have also concluded that benzodiazepines have not been proven effective as SMRs in the treatment of spasticity and musculoskeletal conditions and lumbar radicular syndrome. Furthermore, multiple safety concerns exist regarding the short- and long-term use of benzodiazepines (ranging from central nervous system side effects to increased risk of abuse and dependence).

For more information, please refer to Formulary Status Update – [Benzodiazepines](#)

3. How do cyclobenzaprine, orphenadrine, or other SMRs compare to nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen in the treatment of musculoskeletal conditions?

It is uncertain how any of the SMRs compare to acetaminophen or NSAIDs in the treatment of most musculoskeletal conditions because head-to-head trials have not been conducted. Based on clinical practice guidelines and expert opinion, SMRs (cyclobenzaprine and orphenadrine) may be prescribed

in injured workers for acute or subacute back pain, when first- and second-line agents (acetaminophen and NSAIDs, respectively) have failed to reduce pain sufficiently. In such cases, cyclobenzaprine and orphenadrine should be used for a short course of treatment only (i.e., ≤ 3 weeks).

4. Tizanidine appears to have similar evidence to cyclobenzaprine and orphenadrine for the treatment of short-term acute low back pain (ALBP) and similar evidence to baclofen for the treatment of spasticity. Why isn't tizanidine also listed on the 25WS and 03WS formularies?

Although tizanidine is considered to be similarly effective as cyclobenzaprine and orphenadrine in the short-term treatment ALBP and equivalent to baclofen in the treatment of spasticity, concerns exist regarding safety and cost. Most SMRs are associated with central nervous system side effects (e.g., drowsiness) which may limit their use; however, tizanidine is also associated with cardiac and liver adverse effects that are of additional concern. QT prolongation has been reported with tizanidine use and an increase risk of liver injury have led the manufacturer to recommend regular monitoring of aminotransferase in any individuals prescribed the drug. Tizanidine is also associated with a higher cost of therapy despite the lack of any therapeutic benefit compared to cyclobenzaprine, orphenadrine, and baclofen.

5. What happens to my client who is currently receiving one of these medications paid by the WSIB and whose claim comes up for renewal?

Payment for baclofen, cyclobenzaprine, dantrolene, methocarbamol, orphenadrine and tizanidine will continue for workers who were approved for entitlement prior to the effective date. Brand new requests for these medications will not be approved outside their formulary listing / status. For claims whose drug entitlement comes up for renewal, it is expected that you will use your professional judgment to decide if the worker has benefited from the medication and merits continued use.

[Skeletal Muscle Relaxants](#)

[Health Care Advice: Medications](#)

WSIB RESTRICTED
Please check with your manager before sharing this document externally.

File: Frequently Asked Questions About Tapentadol Controlled Release

Abstract: This is a question and answer document about Tapentadol Controlled Release.

Tags: Nucynta; Frequently Asked Questions; Tapentadol Controlled Release; medications

Last updated: 03/28/2012 03:13:37 PM

Contact: [Tina Papastavros](#)

Author: [Satpal Pannu](#)

Feedback: [Give us your feedback](#)

Questions and Answers - for internal use only

1. Isn't tapentadol controlled release (CR) [Nucynta™] better tolerated than oxycodone CR?

Available evidence from randomized controlled trials (RCTs) indicates that tapentadol CR is associated with lower rates of certain opioid-related side effects than oxycodone CR. However, the high withdrawal rates from these RCTs make it difficult to interpret these results. Furthermore, it has not been determined whether these differences translate into meaningful improvements in functional ability or quality of life.

The adverse event profile of tapentadol CR is similar to that seen with other opioids. Common adverse events reported with tapentadol CR in clinical trials included nausea, vomiting, constipation, headache, dizziness, somnolence, fatigue, and pruritis. No evidence was found relating to the long-term (beyond 15 weeks) safety of tapentadol CR.

2. Has tapentadol CR been compared to other opioids (other than oxycodone CR) in treating CNCP?

There are no RCTs comparing tapentadol CR with less costly formulary alternatives such as long-acting opioid formulations of codeine, morphine, or hydromorphone. While it is not possible to state for certain how tapentadol CR compares with drugs other than oxycodone CR for the treatment of CNCP, tapentadol CR would likely provide comparable analgesia to opioid agonists such as morphine and hydromorphone if given in equianalgesic doses.

3. Does tapentadol CR offer less potential for risk of opioid abuse or misuse?

The abuse potential of tapentadol CR has not been rigorously investigated.

4. Is tapentadol CR effective in treating pain in patients who have failed to respond or have not tolerated other opioids?

There is no evidence that tapentadol CR is effective in treating pain in patients who have failed to respond to or tolerate other opioids. None of the randomized controlled trials investigating the use of tapentadol CR in CNCP specifically assessed its efficacy in opioid refractory or intolerant patients.

5. Doesn't tapentadol CR's dual mechanism of action present an advantage over other opioids that only have one mechanism of action in treating pain?

RCTs comparing tapentadol CR to oxycodone CR in the treatment of CNCP did not demonstrate any advantage in pain relief or function favouring tapentadol CR. This may reflect the fact that tapentadol CR's analgesic effect is mainly attributed to its binding of opioid receptors when administered for the treatment of moderate to moderately severe pain.

6. What are the long-acting opioid alternatives listed on WSIB formularies for treating patients who are diagnosed with chronic noncancer pain (CNCP)?

The following long-acting narcotic agents are listed on WSIB formularies that can meet the treatment needs of workers who require continuous opioid treatment for moderate to moderately severe CNCP:

- Oxycodone (OxyContin®)
- Codeine (Codeine Contin®)
- Hydromorphone (Hydromorph Contin®)
- Morphine (ratio-morphine SR)

The **Narcotic Strategy** should be followed at all times.

7. What is the morphine equivalent dose (MED) for tapentadol CR (Nucynta™)?

A morphine equivalent dose (MED) has not been established. However, clinical studies demonstrated comparable pain relief between tapentadol CR and oxycodone CR at a dose

ratio of 5:1. Therefore,

- each Nucynta™ CR 50mg tablet provides approximately 15mg morphine equivalents
- each Nucynta™ CR 100mg tablet provides approximately 30mg morphine equivalents
- each Nucynta™ CR 150mg tablet provides approximately 45mg morphine equivalents
- each Nucynta™ CR 200mg tablet provides approximately 60mg morphine equivalents
- each Nucynta™ CR 250mg tablet provides approximately 75mg morphine equivalents

8. What happens to my client who is currently receiving tapentadol CR (Nucynta™) paid by the WSIB whose claim comes up for renewal?

Payment for Nucynta™ will continue for workers who were approved for entitlement prior to the effective date. Brand new requests for Nucynta™ will not be approved. For claims whose Nucynta™ entitlement comes up for renewal, it is expected that professional judgment will be exercised to determine if the worker has benefited from the medication and merits continued use. The **Narcotic Strategy** should be followed at all times.

[Formulary Drug Listing Decisions on Tapentadol Controlled Release](#)
[Health Care Advice: Medications](#)
[WSIB Drug Formularies](#)

WSIB RESTRICTED
 Please check with your manager before sharing this document externally.

Title:	Frequently Asked Questions About Targin
--------	--

Abstract: This is a question and answer document about Targin (Oxycodone / Naloxone Controlled Release)

Tags: Naloxone; Targin; Oxycodone; Controlled Release; CR; Oxycontin; FAQ; frequently asked questions; Drug Benefits Program; health care advice; medication; drug; best practices; WSIB Drug Formularies; Health Services Division; opioids; constipation; opioid abuse; misuse; payment for Targin; approval for Targin; Targin renewal; Targin approval.

Last updated: 04/26/2013 11:22:13 AM

Contact: [Tina Papastavros](#)

Author: [Sainal Pannu](#)

Feedback: [Give us your feedback](#)

Questions and Answers - for internal use only

1. In general, is oxycodone / naloxone controlled release (CR) [Targin™] better tolerated than OxyContin®?

The adverse effect profile of oxycodone/naloxone CR appears generally to be similar to Oxycontin® and other opioid agonists, although there was inconsistency across studies in terms of the relative incidences of diarrhea, nervous system disorders and musculoskeletal disorders. In three RCT's comparing oxycodone/naloxone CR to OxyContin®, the incidence of these adverse events were higher in the oxycodone/naloxone arm in one or more trials, but lower in the other(s).

No evidence was found relating to the long-term (beyond 12 weeks) safety of oxycodone/naloxone CR.

2. Is oxycodone/naloxone CR (Targin™) effective in treating pain in patients who have failed to respond or have not tolerated other opioids?

There is no evidence that oxycodone/naloxone CR is effective in treating pain in patients who have failed to respond to or tolerate other opioids. None of the three randomized controlled trials investigating the use of oxycodone/naloxone CR in CNCP specifically assessed its efficacy in opioid refractory or intolerant patients.

3. Is oxycodone / naloxone CR better (Targin™) at preventing constipation than oxycodone plus a preventative bowel routine?

There is no evidence that oxycodone/naloxone CR is better at preventing constipation than oxycodone plus a preventative bowel routine. Although oxycodone/naloxone (at oxycodone doses as high as 80mg/day) appeared to have a measureable effect on outcomes related to bowel function in three 12-week trials, none of these trials compared the medication to a narcotic plus an adequate bowel routine. WSIB formularies list a variety of laxatives that should be used whenever a narcotic is prescribed.

4. What type of preventative bowel routine is recommended in a person prescribed by opioids?

Laxatives are the mainstay of pharmacological therapy in preventing opioid-induced constipation (OIC) and should be used to supplement non-pharmacological therapies (e.g., increasing fibre and fluids in the diet). The following non-prescription products (available on WSIB formularies) would comprise a suitable bowel regimen in the prevention of OIC:

- 100mg of oral docusate sodium twice + 17.2mg of oral sennosides at bedtime as needed.
-

5. Does the naloxone component of Targin™ eliminate the risk of opioid abuse or misuse?

The abuse potential of Targin™ has not been rigorously investigated. Theoretically, the addition of the opioid antagonist naloxone may reduce the risk of parenteral or intranasal abuse (naloxone will precipitate opioid withdrawal when taken by non-oral routes). However, the experience with buprenorphine/naloxone indicates that a certain degree of abuse can occur. Furthermore, given its low oral bioavailability, naloxone will not precipitate withdrawal when taken orally and is less likely to be of a deterrent to the oral abuse of Targin™.

6. What is the morphine equivalent dose (MED) for oxycodone / naloxone (Targin™)?

The MED for Targin™ is based solely on the oxycodone component and is not influenced by the addition of naloxone. Therefore,

- each Targin™ oxycodone 10mg/naloxone 5mg tablet provides 15mg morphine equivalents;
 - each Targin™ oxycodone 20mg/naloxone 10mg tablet provides 30mg morphine equivalents; and
 - each Targin™ oxycodone 40mg/naloxone 20mg tablet provides 60mg morphine equivalents.
-

7. Were there any clinical benefits relevant to WSIB clients, such as quality of life, functional capacity, etc.?

In the three RCT's identified, there was a lack of evidence on endpoints relevant to WSIB clients beyond pain and constipation. Outcomes such as quality of life, functional capacity, and occupational outcomes (eg., return to work, time off work) were not reported.

8. What happens to my client who is currently receiving oxycodone / naloxone (Targin™) paid by the WSIB whose claim comes up for renewal?

Payment for Targin™ will continue for workers who were approved for entitlement prior to the effective date. Brand new requests for Targin™ will not be approved. For claims whose Targin™ entitlement comes up for renewal, it is expected that professional judgment will be exercised to determine if the worker has benefited from the medication and merits continued use.

[Formulary Drug Listing Decisions on Targin \(Oxycodone / Naloxone Controlled Release\)](#)
[Health Care Advice: Medications](#)
[WSIB Drug Formularies](#)

WSIB RESTRICTED

Please check with your manager before sharing this document externally.

Title: Frequently Asked Questions About Tramadol

Abstract: This is a question and answer document about Tramadol.

Tags: Tramadol; pain treatment; tramadol abuse and dependence; Tylenol#3; drug formulary; chronic non-cancer pain med alternatives; CNCP alternatives; status update; medications; Indication; Tramadol; opioids; Health Services; Tramadol; Tramacet; Ralivia; Tridural; Zyltram XL; non-malignant pain; formulary; drug updates; non-cancer; payment for Tramadol; approval for Tramadol; Tramadol renewal.

Last updated: 04/26/2013 11:52:54 AM

Contact: [Tina Papastavros](#)

Author: [Tina Papastavros](#)

Feedback: [Give us your feedback](#)

Questions and Answers - for internal use only

1. I thought tramadol was not classified as an opioid. Why are you comparing it to opioids like Tylenol 3®?

Tramadol has a dual mechanism of action. The parent drug (tramadol) weakly binds to opioid receptors in the brain and also acts by inhibiting norepinephrine and serotonin in individuals suffering from mild pain. In moderate to moderately severe pain, however, tramadol's analgesic effects is mainly attributed to its active metabolite (M1) which acts by binding to opioid receptors.

Tramadol's weak affinity for opioid receptors compared to morphine is often cited as evidence of its lack of opioid activity. However, M1 (tramadol's active metabolite) does not demonstrate a weaker affinity for opioid receptors when compared to opioids such as codeine (a medication demonstrated to be similar to Tramadol in pain relief and adverse events when combined with acetaminophen).

Health Canada does not currently classify tramadol as an opioid. However, the agency has announced its intention to schedule tramadol similarly to opioids or targeted controlled drugs (e.g., benzodiazepines).

2. Doesn't tramadol's dual mechanism of action present an advantage over other pain relievers like traditional opioids that only have one mechanism of action in treating pain?

In populations of interest to the WSIB, we can only draw conclusions regarding the benefit of tramadol's dual mode of action by reviewing the results of randomized controlled trials (RCTs). RCTs comparing tramadol to codeine plus acetaminophen, NSAIDs, and celecoxib in the treatment of CNCP did not demonstrate any advantage in pain relief or function for tramadol. This may reflect the fact that tramadol's analgesic effect is mainly attributed to its binding of opioid receptors when administered for the treatment of moderate to moderately severe pain. Tramadol's ability to inhibit serotonin and norepinephrine re-uptake in the brain may play a more important role in alleviating mild pain. However, opioids are not necessarily the most appropriate agents to use in treating mild pain; hence, tramadol should be compared to non-opioid agents in these patients.

3. I have heard that tramadol does not lead to dependence or abuse. Is this true?

Tramadol appears to have a lower risk of dependence and abuse when compared to stronger opioids like morphine (which may reflect morphine's stronger affinity for opioid receptors). However, it is unclear if tramadol demonstrates a lower risk when compared to weaker opioids like codeine. As tramadol prescribing has quickly expanded, surveillance data have revealed an accompanying increase in reports of dependence and abuse. Indeed, data from the drug abuse warning network of the USA indicate that tramadol's dependence and abuse potential appears to be similar to codeine.

4. Isn't tramadol better tolerated than other opioids, especially when considering side effects like constipation and nausea?

There is a lack of published data accurately providing information on the tolerability of tramadol versus an appropriate opioid comparator like codeine. Two studies that compared tramadol to codeine reported inconsistent results. Tramadol was associated with a significantly lower rate of constipation in one study; yet, the second study reported similar rates of constipation when participants were allowed to take laxatives. Furthermore, some data suggest that tramadol may be associated with higher rates of nausea. When withdrawal rate from trials due to adverse events are examined to gauge tolerability of each treatment, tramadol does not appear to have any advantage. Most trials reported similar withdrawal rates between treatments, with one trial even demonstrating an advantage for codeine plus acetaminophen.

5. Is tramadol a better option in workers who don't respond to Tylenol 3[®] because their pain is too severe or they lack the enzyme that converts codeine to its active metabolite?

Tramadol is indicated in the treatment of patients with moderate to moderately severe pain. In these patients, trials have demonstrated that codeine plus acetaminophen is just as effective as tramadol in reducing pain and improving function. There are no published trials investigating the efficacy of tramadol in the treatment of patients with moderate to moderately severe pain who do not respond to codeine plus acetaminophen. Furthermore, tramadol has never been compared to any opioid analgesic in a well-designed RCT for the treatment of severe CNCP. Given the lack of rigorous evidence, we can not assume that tramadol would be effective in treating patients who have failed an adequate trial of codeine plus acetaminophen.

In patients with moderate to moderately severe pain, tramadol exerts its analgesic effect mainly through the actions of its M1 active metabolite. Tramadol is converted to M1 in the liver by cytochrome P450 2D6 isoenzyme. This is the same enzyme that converts codeine to its active metabolite. Hence, patients who do not experience an adequate response to codeine due to a deficiency in this enzyme (i.e., "poor metabolizers") would experience a similarly blunted response to the analgesic effects of tramadol.

6. What alternative do we currently have on our formularies for the treatment of CNCP?

Various alternative drug classes are currently available on the WSIB formularies. They include:

Nociceptive pain analgesics

- NSAIDs (e.g., diclofenac, naproxen, ibuprofen, etc.)
- Cox-2 Inhibitors (celecoxib)
- Opioids (e.g., Tylenol 3[®], codeine phosphate, Codeine Contin[®])

Neuropathic pain analgesics

- Tricyclic antidepressants (desipramine, amitriptyline, nortriptyline, imipramine)
- Anticonvulsants (e.g., gabapentin)
- Opioids (e.g., Tylenol 3[®], codeine phosphate, Codeine Contin[®])
- Serotonin Norepinephrine Reuptake Inhibitor (e.g., venlafaxine XR).

7. What happens to my client who is currently receiving Tramadol paid by the WSIB?

Payment for tramadol will continue for workers who were approved for entitlement prior to the effective date. New requests for tramadol will not be approved.

[Formulary Status Update on Tramadol](#)

[Health Care Advice: Medications](#)