Formulary Drug Listing Decisions

BENZODIAZEPINES

Indication(s)

Benzodiazepines are indicated in a treatment of a variety of disorders (depending on their pharmacokinetic profile and evidence), including anxiety disorder, panic disorder, insomnia, seizure disorder, muscle spasticity, and alcohol withdrawal.

DAC Recommendation

The Drug Advisory Committee (DAC) has recommended that benzodiazepines NOT be listed as hypnotics or skeletal muscle relaxants; they should continue to be listed ONLY in the 03WS (brain injury), 05WS (burn), 19WS (cancer), 20WS (tinnitus), and 22WS (psychotraumatic) formularies.

The WSIB Decision

Based on the DAC's recommendation, the WSIB has decided NOT to list benzodiazepines as hypnotics or skeletal muscle relaxants. Benzodiazepines will continue to be listed on the 03WS, 05WS, 19WS, 20WS, and 22WS formularies to treat other symptoms/disorders.

Formulary Status

Benzodiazepines are listed in the 03WS, 05WS, 19WS, 20WS, and 22WS formularies ONLY.

Recommendation Highlights

- All benzodiazepines (BZDs) have similar pharmacological profiles but vary in potency and pharmacokinetic properties.
- There is limited evidence to guide the choice of hypnotic for the treatment of *sleep disturbances*. Most studies are small and have methodological limitations.
- The available evidence suggests that there are few differences in efficacy between zopiclone and BZDs. Limited evidence, however, suggests that non-BZDs may be associated with a lower risk of cognitive and psychomotor adverse effects.
- There is no information available comparing efficacy of hypnotic agents in patients experiencing sleep disorders due to a work-related injury on outcomes related to functional ability or productivity.
- There is only limited, poor quality or no evidence for the use of benzodiazepines as *skeletal muscle relaxants* in lower back pain, nonprogressive neurological diseases, spasticity and mechanical neck disorders.
- Prolonged use of BZDs may result in tolerance and the risk of psychological and physical dependence. Benzodiazepines should be used for the shortest duration possible due to lack of evidence for long-term use and safety concerns.
- **The DAC concluded that an independent review of the clinical efficacy, safety, and cost-effectiveness of BZDs in the treatment of insomnia and muscle sprain/spasm indicated that there are alternatives on formulary with better evidence.** Consequently, the DAC recommended that (i) BZDs not be listed as hypnotics or SMRs; and (ii) the appropriate BZDs be listed in the 03Ws, 05WS, 19WS, 20WS, and 22WS formularies **ONLY** to treat other symptoms and disorders.

Drug Profile

Products available in Canada (all available as generics): alprazolam, bromazepam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, flurazepam, lorazepam, midazolam, nitrazepam, oxazepam, temazepam, triazolam.

wsib ONTARIO

DETAILED DISCUSSION

Background

Benzodiazepines (BZDs) are used for a variety of indications, including anxiety, panic disorder, insomnia, seizure disorders, skeletal muscle spasticity, and alcohol withdrawal.

Benzodiazepines work primarily by modulating gamma aminobutyric acid signaling, the major inhibitory neurotransmitter in the central nervous system. All BZDs have similar pharmacological effects. The main difference between BZDs is in their pharmacokinetic properties (onset, metabolism, half-life, etc.) which are usually the guiding factor in drug selection.

Benzodiazepines may be prescribed to treat a variety of symptoms in injured workers. However, concerns exist in the medical literature regarding their long-term use and potential for serious adverse effects and drug interactions.

Summary of Committee Considerations

The DAC considered two external, independent reviews of the clinical efficacy, safety, and cost-effectiveness of BZDs used as *hypnotics* and *skeletal muscle relaxants* (SMRs). The reviews included published and unpublished randomized controlled trials that were at least single-blind, as well as high-quality systematic reviews and meta-analyses.

Two systematic reviews and a meta-analysis compared non-BZD hypnotics (e.g., zopiclone) with BZDs. Both reviews concluded that there are no significant differences between zopiclone and BZDs in sleep-related outcomes or adverse effects. Benzodiazepines showed a significantly greater improvement in sleep duration over zopiclone in one review but the authors concluded that there is insufficient data to prove which drug is superior in the treatment of insomnia. A third high quality systematic review of placebo-controlled trials presented pooled evidence that both non-BZDs and BZDs are more effective when directly compared to placebo. An indirect comparison between BZDs and non-BZDs did not reveal any significant differences between active treatments with respect to sleep onset latency. However, BZDs were associated with a significantly greater risk of adverse effects.

Randomized controlled trials comparing BZDs and non-BZDs have produced similar results (i.e., few differences in efficacy but better tolerability and less psychomotor impairment with zopiclone).

Several systematic reviews have concluded that there is little to no evidence that BZDs are effective as *skeletal muscle relaxants.* A Cochrane Review concluded that although there was strong evidence that non-BZDs are effective in acute low back pain, the evidence is far less convincing for BZDs. Systematic reviews in spinal cord injuries, neurological diseases, and mechanical neck injuries concluded that studies are of poor quality and that BZDs provide marginal or no evidence of clinical benefit. Systematic reviews in spasticity and musculoskeletal conditions and lumbar radicular syndrome also found no evidence of BZD efficacy.

Key guidelines were reviewed to establish standards of care. Hypnotics are generally recommended only after non-pharmacologic measures have been considered, and at the lowest possible dose for the shortest possible duration. There is disagreement over the use of BZDs as SMRs due to the limited evidence. Generally, a limited course of low-dose BZD therapy is reserved for acute pain, after other options have failed.

No pharmacoeconomic studies assessing the use of BZDs as hypnotics or SMRs were located. The Ontario Drug Benefit Program funds various BZDs as general benefits.

Based on the available evidence, the DAC concluded that there was no compelling evidence demonstrating efficacy or safety of long-term use of BZDs as hypnotics or SMRs and that more appropriate alternatives are available. Hence, the DAC recommended BZDs be listed in the 03WS, 05WS, 19WS, 20WS, and 22WS formularies only to treat other symptoms and disorders.

Revised: January 29, 2013