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### **Cold-fX®: “Trust the Science”**

Cold-fX®, manufactured by Afexa Life Sciences Inc. (formerly CV Technologies Inc.), is advertised as the best selling cold and flu remedy in Canada and was recently designated the official cold and flu remedy for the 2010 Winter Olympics.<sup>1</sup> It has been approved by Health Canada to help reduce the frequency, severity and duration of cold and flu symptoms by boosting the immune system but not for acute treatment of these conditions.<sup>2</sup>

Cold-fX® is derived from the root of North American ginseng (*Panax quinquefolius*).<sup>3</sup> The root contains a variety of ginsenosides, polysaccharides and oligosaccharides.<sup>3</sup> Immunomodulating effects of North American ginseng are thought to be due to its polysaccharide and oligosaccharide content.<sup>3</sup> The medicinal ingredient in Cold-fX®, CVT-E002™, is a standardized extract of North American ginseng consisting primarily of poly-furanosyl-pyranosyl-saccharides.<sup>1</sup> Because it has little or no ginsenoside content, CVT-E002™ is claimed to have a lower risk of the adverse effects associated with other ginseng products.<sup>1</sup>

#### **Mechanism of Action:**

Cold-fX® is purported to exert its effect by enhancing the innate and acquired immune system functions.<sup>1</sup> In laboratory studies of CVT-E002™, it has been shown to activate several components of the immune system but exactly how these effects would reduce the severity of symptoms remains unclear.<sup>4,5</sup>

#### **Evidence of Effectiveness:**

Claims regarding the effectiveness and safety of Cold-fX® are based on several studies all funded by the manufacturer.<sup>1</sup> Three (arguably four<sup>6</sup>) of these studies are randomized placebo controlled trials (RCTs). (Table 1)

The most recently published study was actually the first RCT of Cold-fX®. Carried out in 1998, it was essentially a pilot study involving a small number of community-living seniors. The study suggested Cold-fX® might reduce the incidence, frequency, and duration of symptoms of acute respiratory infections (ARIs) in immunocompetent seniors after immunization with influenza vaccine.<sup>7</sup>

In 2000 and 2001, two trials were conducted with seniors living in long-term care facilities. Neither of these studies showed a significant reduction in the incidence of ARIs. The authors combined the results of these studies in the published article. The primary endpoint, clinically confirmed ARI, was still not significant for a difference between Cold-fX® and placebo. The secondary end-point, laboratory confirmed ARI, suggested a potential benefit with Cold-fX® but requires confirmation.<sup>8</sup>

A larger RCT involving younger subjects (18 – 65 years of age) was undertaken in the winter of 2003-2004.<sup>9</sup> There was no reduction in the incidence of the first cold experienced by subjects but

there was a small but statistically significant reduction (12.8 %) in the incidence of subsequent colds over the 4 month study period. Based on this figure, only one out of eight people taking Cold-fX® for 4 months would benefit by not experiencing more than one cold during this period. The authors also reported that Cold-fX® reduced the severity and the duration of cold symptoms; however these were secondary endpoints so these claims require confirmation. Concerns regarding the methodology of this study include self-reporting of symptoms, use of an unvalidated modification of the Jackson cold definition to identify cases and no laboratory analysis to differentiate between colds and influenza.<sup>10</sup>

A systematic review of published literature on the efficacy of Cold-fX® and other North American or Asian ginseng root extracts in reducing the incidence of colds was recently published. Out of 722 citations identified in the electronic database search, only four articles met the review criteria. Three of these were the Cold-fX® studies described above. The fourth study used Ginsana G115® (an extract of *Panax ginseng*) as the intervention. Meta-analysis of these studies was non-significant for a difference between the ginseng extracts and placebo. The authors state that there is insufficient evidence to conclude that ginseng reduces the incidence of common colds.<sup>11</sup>

Further studies of Cold-fX® are being funded by the manufacturer. One is a large study involving 720 community-dwelling seniors in three cities, Toronto, Edmonton and Vancouver. The primary outcome is prevention of laboratory-confirmed flu and cold viruses. No results are available at this time.<sup>12</sup>

#### **Evidence of safety:**

The safety of Cold-fX® has not been directly studied but all of the RCTs tracked adverse effects. There were no significant differences in the incidence of adverse effects between treatment and placebo groups. The most common effects reported were gastrointestinal symptoms.<sup>11</sup>

#### **Summary:**

Given the limited and conflicting evidence from low quality trials, more study is needed to fully evaluate the benefits and risks of Cold-fX® .

- Current evidence supports at best, a very modest reduction in the incidence of multiple colds in healthy adults between 18 and 65 years. This is based on one study with questionable methodology. These results cannot be generalized to other population subgroups such as persons with chronic medical conditions, children, pregnant or lactation women.
- Benefit for seniors, community-living and institutionalized has not been demonstrated. A pilot study of community-living seniors and secondary outcomes of the RCT involving institutionalized seniors raise hypotheses about potential benefits but further study is needed.
- Claims that Cold-fX® 400 mg daily taken regularly reduces the severity and duration of cold symptoms are based on secondary outcomes and require confirmation.. No studies of the effect of short-term high-dose Cold-fx® for acute treatment of ARI symptoms have been published.
- Cold-fX® appears to be safe when used by healthy adults at a dose of 200 mg twice daily for up to 4 months.

## References:

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**Table 1: Randomized Placebo Controlled Trials of Cold-fX®<sup>7,8,9,11,13</sup>**

Study	Subjects	Cold-fX® 2 X 200 mg daily	Placebo	Primary outcome	Results / Comments
McElhaney et al., 2004	Mean age 82 – 83.5 yrs Long-term care facility	N = 97 8-12 wks	N = 101	Reduction in clinically confirmed ARI	Primary outcome - N.S. Secondary outcome – 89 % reduction in laboratory confirmed ARI (CI 14 – 99 %)
Preedy et al., 2005	Mean age 43 years Community-living	N = 130 16 wks	N = 149	Reduction in number of Jackson-verified colds	One cold – NS 2 or more colds ARR = 12.8 % (CI 4.3-21.3 %) NNT = 8 (CI 5 – 23).
McElhaney et al., 2006	Mean age 69 yrs Community-living	N = 22 16 wks	N = 21	Reduction in incidence of ARI, duration of ARI symptoms	Preliminary study; no calculation of power. Results suggest the incidence of ARI decreased by 30 % and duration of symptoms decreased by 55% in last 8 weeks of treatment

ARI = acute respiratory infection; ARR = absolute risk reduction; NNT = number needed to treat