# Actovegin® — Cutting-edge Sports Medicine or "Voodoo" Remedy?

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**Abstract**

Actovegin® is a deproteinized serum extract of bovine origin, and in recent years it has been used widely in treating sport injuries with many anecdotal reports of success. However, the use of Actovegin® in sport medicine has caused a substantial amount of controversy, especially concerning its supposed oxygen-enhancing capacity and an anecdotal belief that its use can increase an athlete's performance. In 2009, a sports physician was arrested with this "performance-enhancing drug," while an editorial in a sports medicine journal strongly questioned the evidence base for using this drug for acute muscle injury. There is also a report that suggested that Actovegin® might have induced anaphylactic shock in a cyclist. In this review, we have systematically examined the current evidence on Actovegin®. Its mechanism of action, clinical evidence, legal status with sports governing bodies, and its potential role in sport injuries will be discussed.

## Introduction

Actovegin® has received a great deal of media attention in the recent years, especially surrounding its use in sports medicine. In 2009, a sports physician was arrested with this performance-enhancing drug, whereas an editorial in a sports medicine journal strongly questioned the evidence base for using this drug for acute muscle injury (12). There is also a report that suggested that Actovegin® might have induced anaphylactic shock in a cyclist (20). However, there also are good safety results from a large, multicenter, randomized, control trial (36). Nevertheless, Actovegin® has received much publicity, and there also are many anecdotal beliefs surrounding this drug (12). Currently, Actovegin® is not on the World Anti-Doping Agency's (WADA) prohibited substance list (34). However, many athletes, coaches, and doctors still have reservations about its use in sports medicine. In this article we review the evidence of the efficacy of Actovegin® as a drug and discuss its potential role in sports medicine.

## Methods

A comprehensive literature search was performed on MEDLINE (1950 to 2010), PubMed, Embase (1980 to 2010), the Allied and Complementary Medicine Database (1985 to 2010), ScienceDirect, Scopus, BIOSIS, the Cochrane Library, and Google. The title, abstract, and key words were searched using the terms "Actovegin®," "injection therapy," and "muscle injuries." No language restrictions were imposed; original articles were obtained if possible and translated to English. Only relevant articles were included in this review after discussion between the authors.

## Background

Actovegin® is a deproteinized hemodialysate of ultrafiltered calf serum from animals under 8 months of age, produced by Nycomed GmbH, Linz, Austria. Austria is officially categorized as a bovine spongiform encephalopathy-, transmissible spongiform encephalopathy-, and scrapie-free country by the World Organization for Animal Health and the Scientific Steering Committee of the European Union. The manufacturing process of Actovegin® is bovine spongiform encephalopathy validated, thus proven to be capable of removing hypothetically present transmissible spongiform encephalopathy agents (23). It is ultrafiltered to 6,000 Da; therefore, it does not contain protein, growth factors, or hormonelike substances. Actovegin® contains physiological components, electrolytes, and essential trace elements. Amino acids, nucleosides, and intermediary products of carbohydrate and fat metabolites constitute approximately 30% of organic components in Actovegin® (23). The active ingredients in this mixture have yet to be identified. Actovegin® can be administered as tablets, topical formulations, injections,

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or infusion via intramuscular, intravenous, or intra-arterial routes (23).

Actovegin® is a licensed drug in Europe, China, and Russia and has been used by clinicians for more than 60 yr (3,23,28,35). Clinically, it has been used as an intravenous infusion to treat acute stroke (5,11) and as a topical form to treat skin and mouth ulcers (4). It also has been reported to be used as an intra-arterial infusion to treat long-bone fractures (17) and postpartum hemorrhage (2). Solcoseryl (Valeant Pharmaceuticals International, Moscow) is another widely used drug in the same calf serum hemodialysate group, but there has been no published report comparing the ingredients or biological actions between Actovegin® and Solcoseryl. In this review, we will only focus on the evidence around Actovegin®.

## Mechanisms

During the past 60 yr, researchers have endeavored to identify the active ingredients in Actovegin® but have been unsuccessful. Studies *in vitro* have suggested that it promotes oxidative metabolism and shifts the redox balance of cells into the direction of oxidized substrates. Actovegin®, therefore, initially was thought to have protective effects against hypoxic cell injury (30). Hoyer and Betz (14) demonstrated that Actovegin® does not directly influence cells during the ischemic period because the intracellular levels of glucose and lactate are similar to untreated animal cells during this period. Therefore, its mechanism of action is thought to improve the efficacy of a cell's energy balance in the postischemic metabolic events and interrupt the process of cell damage to avoid further cell death (14).

Inositol phosphate oligosaccharides (IPO) are one of the putative ingredients in Actovegin® (24). The IPO have been shown to have a partial insulin-like effect on the glucose transport activity of adipocytes but do not induce carrier translocation or stimulate insulin receptor kinase *in vitro* or *in vivo* (24). It has been reported that IPO activate glucose transporters, hence promoting glucose uptake by cells (10). IPO can contribute up to 50% of the maximum insulin effect on glucose transport and also can stimulate the activity of certain enzymes including pyruvate dehydrogenase, the key enzyme of the citric acid cycle (24). It has a synergistic effect with insulin and promotes glucose activity when insulin levels are suboptimal but does not alter the peak effect (24). A strongly negatively charged sulfated oligosaccharide of approximately 3,000-Da molecular weight also has been isolated from Actovegin®, which is different from the IPO fraction reported by the other studies (30). This fraction has a similar effect to IPO but with less effectiveness.

Actovegin® has a synergistic effect on cell proliferation *in vivo* with epidermal growth factor, basic fibroblast growth factor, and endothelial cell growth factor, causing an increase in cell numbers, an increased activity of acid phosphatase, and an improved level of thymidine incorporation compared with controls (30). These effects are resistant to proteinase K digestion; therefore, the active compounds of Actovegin® are unlikely to be growth factors or their derived fragments (30). The trivial nutritive effects of Actovegin® were excluded because a mixture of the same level of amino acids and substrates did not stimulate proliferation or have insulin-like activity *in vivo* (30).

Actovegin® is likely to have membrane-stabilizing effects in ischemic cells. This may be due to the presence of negatively charged oligosaccharides, shifting the cells to the direction of oxidized substrates. At the immediate postischemic period, these factors may help cellular recovery. Its insulin and growth factor synergistic properties also could be beneficial and make the initial recovery period more efficient. Therefore, Actovegin® is assumed to be useful in circulatory disturbances and postischemic events.

A recent study *in vivo* indicated that Actovegin® could regulate the expression of cell surface receptors on macrophages, which indicates their phenotypic subgroups in the inflammatory sequence leading to muscle repair (18). Furthermore, Actovegin® can upregulate some of the inflammatory mediators that may have an important role in regulating the inflammatory process in muscle healing (18).

### Clinical Reports Not Related to Muscle Injuries

Although the active ingredients in Actovegin® are yet to be identified, many clinical studies have indicated its safety and effectiveness. There has been one case report of a possible anaphylactic reaction related to the use of intravenous Actovegin® injections by an amateur cyclist. In this report, the diagnosis of "anaphylactic reaction" was not confirmed with any biochemical testing, and the patient improved with broad-spectrum antibiotics. The author later stated in the communication letter that this patient had used intravenous Actovegin® once before with no adverse reaction; thus, an anaphylactic response is unlikely. However, it is possible that the first use of Actovegin® has primed the immune cells to react severely after the second or subsequent administrations. Because the patient improved on broad-spectrum antibiotics, the most likely cause for this acute shock was due to bacterial contamination during injection, not anaphylactic reaction to the drug (20).

Pforringer *et al.* (28), in a double-blind, placebo-controlled, single-center study with 60 recreational athletes, demonstrated that ultrasound-guided paratenon injection of Actovegin® was effective in the treatment of Achilles tendinitis. The tendon cross-sectional measurement was reduced significantly ($P < 0.0001$); patients' physical activity and perception to pain also were improved ($P < 0.002$) in the treatment group (28). The overall clinical outcome, which is measured by patients' satisfactory score, was significantly better in the Actovegin® group ($P < 0.0001$), and no adverse event was reported in this study (28). Although it is a relatively small-scale study with limited power, it is a well-conducted study that was featured in a Cochrane Review. Ziegler *et al.* (36) reported a double-blind, multicenter, randomized, control study with 567 patients with type 2 diabetes, in which 281 patients were treated with 20 daily high-dose intravenous Actovegin® infusions followed by 1,800 mg of Actovegin® daily for 120 d in the treatment of symptomatic diabetic polyneuropathy compared with placebo. Total symptom score of the lower limbs, vibration perception threshold, Neuropathy Impairment Score of the Lower Limbs, and quality of life (SF-36) were used as patient-reported outcome measures, which all showed a statistically significant difference compared with placebo

and baseline scores ($P < 0.05$). Furthermore, no anaphylactic reactions were reported with this study after 5,620 infusions, and the adverse effect profile was no different compared with placebo (36).

## Legal Status

Besides its clinical properties, there are anecdotal beliefs among athletes that Actovegin® possesses an oxygen-carrying capacity and has the potential to enhance oxygen uptake, which leads to better performance. Although these claims are not based on any objective scientific evidence or published clinical reports, the International Olympic Committee announced in December 2000 that Actovegin® was banned under the classification of blood-doping agents. Two months later, however, the International Olympic Committee lifted the ban because there was no evidence that Actovegin® actually enhances performance (32). So far, there have not been any sports-related studies or performance testing with this drug on healthy individuals. Currently, intramuscular use of Actovegin® is not prohibited in or out of competition for any given sport according to the latest search (2010) in the Global Drug Reference Online, which is approved by U.K. Anti-Doping, the Canadian Centre for Ethics in Sport, the U.S. Anti-Doping Agency, and WADA (13). According to the latest 2011 WADA prohibited list, Actovegin® is not prohibited in any sports. However, WADA has issued a specific guidance on Actovegin® on its Web site. According to section M2 of the WADA code, the volume of intravenous injection of any nonprohibited substance must not exceed 50 mL with a simple syringe, and further serial injections must be at least 6 h apart (34). Therefore, it should be stated clearly here that Actovegin® cannot be administered by intravenous infusion or single intravenous injection with a volume exceeding 50 mL (34).

## Muscle Injuries

Muscle injuries are one of the most common sports-related injuries; their incidence varies from 30% to 55% (15,22,33). Rest, immobilization (15), physical therapy (7), and nonsteroidal antiinflammatory drugs (NSAID) (29) have been the mainstay of therapy for muscle injuries (16). Immobilization may lead to improved granulation of the injured muscle and promote healing, but it will cause significant atrophy of healthy myofibers and joint stiffness (15). Although some studies have shown that the administration of NSAID promotes muscle healing by reducing degeneration and inflammation, other studies have demonstrated that NSAID are detrimental to the entire healing process (1,21,25,31). Recently, new treatment options such as growth factor injection therapy have shown good therapeutic results. However, because of their performance-enhancing properties, growth factor hormones are prohibited by WADA under sections M1 and S2 from the WADA prohibited list (34). In 2008, Orchard *et al.* (26), in a best practice statement, suggested that the evidence on current treatments in muscle injuries is low; further research in new treatment such as Dr. Müller-Wohlfahrt's Actovegin® and Traumeel (Heel, Inc., New Mexico) injection therapy should be explored.

A recent comprehensive review of the cellular and molecular mechanisms of muscle regeneration suggested that muscle repair after muscle strains is initiated by necrosis. Posttraumatic necrosis of the myofibers stimulates an inflammatory response mediated by macrophages (8). This, followed by differentiation of satellite cells then maturation, leads to new myofiber formation (8). This process is different from the sequence of events observed during embryonic myogenesis.

Macrophages traditionally have been viewed as scavengers only involved in the removal of necrotic debris; however, recent studies have suggested that they also may have an active role in promoting muscle regeneration (8,18). Muscle fiber necrosis leads to dissolution of the plasma membrane causing rapid disintegration of myofibrils (8). This activates the complement cascade causing chemotaxis of leukocytes and monocytes from blood. Recent studies suggest that there are two distinct subpopulations of macrophages sequentially involved in this process (8). The early invading "phagocytic" macrophages ($CD68^+$), characterized by the expression of the CD68 cell surface marker and lacking the CD163 marker, reach the highest concentration in damaged muscle at about 24 h after the onset of injury and then rapidly decline. These $CD68^+$ macrophages are proinflammatory phagocytes that secrete inflammatory cytokines such as the tumor necrosis factor and interleukin-1 and are responsible for the removal of necrotic debris. After 48 h, a second subpopulation of "nonphagocytic" macrophages ($CD163^+$), characterized by the expression of the CD163 surface marker and lacking the CD68 marker, was then found and reaches a peak at day 4 after the initial injury. This $CD163^+$ subgroup displays an antiinflammatory property and secretes cytokines, such as interleukin-10, which contributes to the termination of inflammation (6,8).

Therefore, macrophages have a central regulatory role in the muscle response to injury (6,8). A recent report suggested that Actovegin® may cause up-regulation of the $CD68^+$ subgroup of macrophages and the precursor of the $CD163^+$ subgroup *in vitro* (6,8,18). However, it is only a preliminary laboratory-based gene expression report; it may or may not translate to clinical practice. Therefore, premature conclusions must not be drawn until more research is published in this area.

## Evidence on Actovegin® in Muscle Injuries

The treatment of muscle tears with intramuscular Actovegin® was first published by Pfister and Koller (27) in 1990. Their partially blinded case control study with 103 patients showed a reduction of recovery time with the treatment group of 5.5 wk compared with 8.3 wk for the control group (27). However, in this study, patients were recruited from various sports and levels, and the treatment regimen and the rehabilitation protocol were not standardized. The diagnosis of muscle injuries was based only on clinical findings and was not graded according to magnetic resonance imaging. Actovegin® was mixed with local anesthetics before injection; therefore, its pharmacodynamics and pharmacokinetics were altered. The treatment regimen in this study was not standardized, the number of injections ranged from three to eight, and the final outcomes were based on patients' and various clinicians' subjective observations, and there were no preinjury data to compare outcomes. Despite

the limitations of the study, it is the first published study regarding Actovegin's use as an intramuscular injection in the treatment of muscle injuries, and no adverse events were reported in this article. Since Pfister and Koller (27), there had not been any published report in the medical literature regarding the use of Actovegin® in muscle injuries until Wright-Carpenter *et al.* (35) in 2004. In this small nonrandomized study, autologous conditioned serum was compared with Actovegin®. The Actovegin® group in this study was created by the retrospective analysis of the study of Pfister and Koller; therefore, it should not be seen as new evidence.

Ziegler *et al.* (36) reported a double-blind, multicenter, randomized, control study with 567 diabetic patients treated with Actovegin® for diabetic neuropathies, which was discussed above. Although muscle assessments were not the primary objective for this study, it was measured as a secondary objective to monitor the progression of treatment. There was no significant difference in the adverse event rate compared with placebo; Actovegin® did not improve muscle strength ($P = 0.731$) or muscle reflex ($P = 0.571$) (36). Therefore, it is reasonable to conclude that Actovegin® is a safe drug and does not have anabolic or ergogenic effects on muscles.

Lee *et al.* (19) reported the first single Actovegin® intramuscular injection therapy on high-level professional footballers. The therapy regimen described by Lee *et al.* for magnetic resonance imaging-proven grade I hamstring injuries seems to significantly reduce the number of days for return to play, with a mean of 8 d of reduction compared with rehabilitation therapy alone ($P < 0.05$). Although this is an observational study with only 11 subjects and without a placebo injection group, potential psychological effects of injection cannot be ruled out. Nevertheless, this study provided important pilot data regarding the use of single Actovegin® intramuscular injection therapy for muscle injuries.

## Discussion

*In vivo* and *in vitro* studies suggest that Actovegin® contains some active components, although they are yet to be identified. It is a licensed drug that has been used by clinicians across Europe, China, and Russia to treat stroke and diabetic neuropathies (4,17,23,28,35). There is limited evidence on its role regarding the treatment of muscle injuries and no evidence regarding any performance-enhancing properties (27). Recently, there have been *in vitro* research data suggesting that Actovegin® may have a role in the modulation of the inflammatory process in muscle repair after traumatic injuries (6,8,18).

An unpublished case series with high-profile sports people such as Maurice Green, Asafa Powell, Diego Maradona, Darren Gough, and Paula Radcliffe suggested that Dr. Hans-Wilhelm Müller-Wohlfahrt's injection regimen with a mixture of Actovegin®, Traumeel, and local anesthetics seems to have good anecdotal results (9,26). There has been only one small clinical study investigating the effect of standalone Actovegin® therapy in muscle injuries. Our review describes the clinical use and evaluation of Actovegin® for more than 60 yr with an apparently good safety profile. The only anaphylactic case report published could be discounted because the cause is most likely to be bacterial contamination of the injection site. Actovegin® does not improve muscle strength or muscle reflex, and there is no evidence of an ergogenic effect reported.

The mechanism of action with Actovegin® can potentially protect ischemic cells, modulate the inflammatory process, and help the initial phase of recovery from acute muscle injuries become more efficient. Skeletal muscle is a very vascular structure and is highly energy dependent. Once injured, blood flow often is disturbed, which leads to cell ischemia and energy imbalance. Therefore, Actovegin® injection therapy to the injury site might aid recovery and limit further ischemic effects and control cellular damage from the initial injuries.

Official governing bodies including WADA, U.K. Anti-Doping, the Canadian Centre for Ethics in Sport, and the U.S. Anti-Doping Agency do not prohibit its use intramuscularly. On the other hand, it is not on the British National Formulary, and the Medicines and Healthcare products Regulatory Agency in the United Kingdom and the Food and Drug Administration in the United States have not approved its use. Although it is not uncommon in modern medical therapy, the intramuscular use of Actovegin® to treat muscle injuries is off-license.

In professional elite-level athletes, Orchard *et al.* (26) summarized that currently, almost all our so-called knowledge in the treatment of muscle injuries was based on very poor scientific evidence. The career lifespan for the professional elite athlete often is short-lived; shortened recovery time could mean continuing with training, increased game play, and benefit to the team and club.

Because of the unique relationship between sports physicians and athletes, they often are under pressure to seek the latest "active" or "cutting-edge" treatments (12). Athletes often are not interested in being part of a clinical trial. Therefore, it is not always possible to get a large number of participants who are professional athletes. There is also much publicity about the use of this drug on the basis of anecdotal assumptions on its questionable theoretical ergogenic properties and placebo effects (12). To obtain the highest level of evidence and rule out placebo effects with intramuscular Actovegin® therapy, a control must be established first. Because the traditional treatment of muscle injuries is based on low-level evidence, there has not been any report or evidence on intramuscular isotonic saline injection therapy. Therefore, it is unethical to assume that intramuscular isotonic saline is a placebo and can be used as control group. Nevertheless, Actovegin® is not licensed to treat muscle or soft tissue injuries, and its evidence is limited. There is published evidence demonstrating its efficacy and safety for a variety of conditions not related to muscle injuries (2,4,5,17,28,36).

As modern sports physicians, we must apply the principles of evidence-based medicine when considering new therapies. Physicians should process these evidences carefully and pay attention to detail, especially when the published medical literatures are limited. This article summarizes the current evidence on Actovegin®. Through our research, there is no evidence that Actovegin® can enhance an athlete's performance. Further research must be encouraged to investigate the effects of Actovegin® on muscle injuries before

it can be labeled as an effective treatment. Injection therapy could potentially be useful in the treatment of muscle injuries; therefore, it should not be regarded as a "witchcraft" remedy. Currently, Actovegin® falls somewhere in between cutting-edge and "voodoo."


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