Product Monograph

Traumeel®

Strong on inflammation, gentle on patients

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Traumeel®

1 Overview

Traumeel® has been used in more than 50 countries around the world for over 60 years, having reached millions of patients with a usage of over 10 million packages a year, of which more than half are ointment and gel.

Acute musculoskeletal injury accounts for a substantial burden on healthcare services and patients, and is a leading cause of absence from work. While inflammation is a crucial part of the healing process, excessive inflammation can be detrimental to recovery. Successful management of acute musculoskeletal injury requires early recognition, identification of the cause and treatment of any specific pathology. However, even the most accepted treatments for acute musculoskeletal injury find little support when critically evaluated.

Traumeel® has been proven effective in the treatment of acute musculoskeletal injury and inflammation. It is indicated as a first-line treatment for patients with traumatic injuries of all kinds such as sprains, dislocations, contusions, hemarthrosis and effusions into a joint; regulation of inflammatory processes in various organs and tissues, including in particular acute and chronic/degenerative disorders of the musculoskeletal system.

Traumeel® contains 14 components from natural sources combined to cover the different aspects of the inflammatory phenomenon. It has a different mode of action to conventional anti-inflammatory drugs, and appears to work through complex interactions with the cytokine network, which regulates inflammatory responses. The components of Traumeel® act synergistically to accelerate the process.

Randomized controlled studies have shown that Traumeel® is significantly more effective than placebo and at least as effective as diclofenac in the treatment of musculoskeletal injury. Observational cohort studies have shown Traumeel® to be at least comparable with conventional therapies in terms of resolution of symptoms and time to symptomatic improvement.

Recently, in a large multicenter randomized controlled trial, the Traumeel® in Acute Ankle Sprain Study (TAASS) demonstrated that Traumeel® ointment and gel is an effective alternative to topical diclofenac 1% gel in the treatment of ankle sprain. This has further added to the evidence-base for the use of Traumeel® in musculoskeletal injuries. In view of the results from TAASS and the established evidence base, a treatment algorithm has been developed to assist clinicians in the appropriate utilization of Traumeel® in clinical practice.

Osteoarthritis is the most common form of joint disease, with prevalence increasing with age. The effects of subclinical chronic inflammation in osteoarthritis are now increasingly recognized. Osteoarthritis can cause considerable burden to the patient, carers and healthcare systems. The recent MOZArT study, a large randomized controlled trial, demonstrated that the co-administration of intra-articular injections of Traumeel® and

Zeel® T is effective in reducing the pain associated with osteoarthritis of the knee.

Safety studies have indicated that Traumeel® is unlikely to interfere with antimicrobial first defenses, the normal homeostatic process, kidney function or liver function. Post-marketing surveillance has demonstrated very good tolerability for Traumeel® formulations with very few adverse effects.

Indeed, tolerability of Traumeel® has been demonstrated to be significantly greater than with conventional treatments.

Investigation of the efficacy and place in therapy of Traumeel® is ongoing with further randomized controlled trials underway.

Traumeel® is suitable for most patients requiring first-line treatment for musculoskeletal injuries and inflammation. It may be particularly suitable for patients who are unable or unwilling to tolerate conventional anti-inflammatory medication, or for those in whom such treatment is contraindicated.

Traumeel® is registered as a Homeopathic Medicinal Product for the treatment of musculoskeletal injuries and inflammation.

2 Musculoskeletal disorders

There are many disorders affecting the musculoskeletal system. Traumeel® has been proven to be effective in the treatment of musculoskeletal injuries and, when co-administered with Zeel® T, osteoarthritis.[1,2,3]

Musculoskeletal injuries

Structure of soft tissue

Collectively, injuries to tendons, ligaments and/or skeletal muscle, are referred to as musculoskeletal soft tissue injuries.[4]

Tendons and ligaments are common structures that can be injured as a result of participating in physical activities or specific activities in the workplace.[4] Tendons are collagenous structures with additional tenocytes, water and other matrix components.[5] Some tendons have tenosynovial sheaths, particularly those travelling through narrow areas such as in the hands and wrist, or the ankle.[6] Ligaments have a similar structure to tendons, but they do not have sheaths.[6]

In skeletal muscle, bundles of muscle fibers are enclosed by the perimysium to form fascicles. These in turn are gathered together within the epimysium to form muscle. There are more than 430 voluntary muscles in the body. Skeletal muscle has an extensive and complex blood supply that can be improved by physical training.[6]

In addition, soft tissue includes bursae, which are fluid-filled sacs to minimize friction between adjacent moving structures, and joint capsules, which consist of fibrous collagenous tissue with some synovial lining.[6]

KEY FACT

Musculoskeletal injuries are a common reason for sickness absences from work.

Epidemiology of musculoskeletal injury

A lack of universally acceptable diagnostic criteria for many soft tissue disorders makes the epidemiology of such complaints difficult to establish. However, while the precise incidence and prevalence of such disorders are difficult to define, they are known to be the most common rheumatic causes of sickness absences from work.[6] Indeed, soft tissue complaints account for up to 59% of new patient referrals to rheumatology practice and up to 15% of consultations in primary care.[5]

Ankle injuries are very common with an estimated incidence of 1 per 100,000 population per day.[7] They account for about one in five of all sports-related injuries. The majority of ankle injuries are moderate ligament sprains. With appropriate treatment the majority of patients should be able to return to normal activities within a few weeks.

KEY FACT

Soft-tissue injury produces a non-specific physiologic response that activates a series of pro-inflammatory events.

Knee injuries can be particularly concerning, especially those affecting the anterior cruciate ligament, as they can cause lengthy absence from normal activities, such as work and physical exercise.[7] The highest incidence of anterior cruciate ligament injuries is seen in young physically active people between 15 and 25 years of age. The incidence is 3 to 5 times higher in women than men. Injury is commonly caused by rotation of the knee, and may be consequence of physical activities such as football, basketball and skiing.

Tendinothies can result in appreciable morbidity and loss of productivity, representing a major socioeconomic burden.[5] Trigger finger, tennis elbow, Achilles' tendinopathy, and rotator cuff lesions are some of the most common tendinopathies.[5] It is interesting to note that more tennis elbows probably result from industrial work, gardening, or carpentry than from sport.[8] Pain and dysfunction are the main symptoms of tendinopathy, while clinical signs such as swelling or thickening of the tendon are variable.[5]

Classification of musculoskeletal injuries

Periarticular soft tissue complaints include localized disorders of tendons, ligaments, muscles, fascia, and joint capsules.[5]

Musculoskeletal injuries can be classified according to the duration of symptoms. Up to 2 weeks, symptoms may be described as acute, 2–4 weeks may be described as subacute, and if symptoms have been present for over 6 weeks, the condition may be described as chronic.[5]

Traumatic soft tissue injuries may also be classified as macrotraumatic or microtraumatic. A macrotraumatic injury involves a single episode of acute tissue destruction, while a microtraumatic injury involves either chronic overload or an acute-on-chronic episode.[6]

Acute exacerbations of chronic disorders occur when a chronic disorder flares to produce acute symptoms. These should be managed as an acute injury with additional regard to the underlying condition and its long-term management in order to prevent further flares.

Tissue response to acute injury

After acute injury, inflammation is the body's method of limiting the amount of tissue damage and protecting against further insult.[9] Injury of soft tissue results in a non-specific physiologic response that activates a series of pro-inflammatory events (see Table 1, page 9). The zone of the primary injury is defined by the extent of the initial hematoma. However, more cell damage can occur from the edema and tissue hypoxia resulting from the acute vascular inflammatory response. This is referred to as the 'secondary zone of injury'.

Table 1
Physiologic response to soft tissue injury.[9]

- Immediate vasoconstriction limiting local hemorrhage followed by subsequent vasodilatation and an increase in vascular permeability near the site of injury
- Platelets adhere to one another at the site of capillary damage to provide a mechanical plug to prevent further bleeding
- Activation of the clotting cascade results in the formation of fibrin and fibronectin, which form cross-links with collagen to reinforce the temporary plug and stop hemorrhage
- Pain-producing chemical mediators including bradykinin, serotonin and histamine are released and aid in the attraction of leukocytes to the site of injury
- Leukocytes (neutrophils, eosinophils, basophils, macrophages and lymphocytes) balance clotting and anticoagulation, stimulate local edema, clear debris and have immunologic functions

KEY FACT

The inflammatory process contributes to healing once the initial inflammatory response subsides.

After the initial inflammatory response (usually within 24 hours), the inflammatory process becomes a healing process.[9] Damaged tissues are cleared by phagocytosis and the foundation is laid for new tissues. As phagocytosis is nearing completion (normally after several days), the proliferation phase of healing begins. Fibroblasts and granulocytes are drawn to the site of injury by growth factors, and new collagen is produced to replace the injured tissues.

Within a few days of trauma, a new network of capillaries is established to ensure that scar tissue is well vascularized.[9] As new tissue is constructed, the original scar tissue is being dissolved. The scar eventually decreases in size, and tissue remodeling occurs according to the specific demands placed on the healing tissues. Complete scar maturation may take up to 1 year.

Factors affecting response to injury

For successful management of acute soft tissue injury factors promoting efficient optimal recovery should be maximized.[6] For example, early controlled activity is helpful, but excessive activity may impair recovery. Nutrition is also important, and an adequate intake of protein, energy, vitamins and minerals is required. Inflammation, while part of the healing process, can be deleterious if excessive.

Other factors that can affect the healing process are difficult to modify, but should still be factored into the management process to improve outcomes. For example, tissues take longer to heal with increasing age, partly as a result of morphological and biochemical changes in collagen and elastin fibers.[6] A poor vascular supply may be an important factor in the chronic evolution of soft tissue injuries such as tendon disorders.

KEY FACT

The paradigm underlying the successful management of acute musculoskeletal injury is to control pain so that rehabilitation can proceed.

Endocrine disorders can also have an impact on healing. A poor healing response in diabetes is well recognized, and hypoestrogenism may be associated with an increased incidence of tendinosis.

Genetic factors are implicated in the etiology of many acute musculoskeletal soft tissue injuries.[4] Common musculoskeletal soft tissue injuries for which a genetic contribution has been proposed include the Achilles tendon in the heel, the rotator cuff tendons in the shoulder and the cruciate ligaments in the knee.

Current treatment options

Successful management of acute musculoskeletal injury requires early recognition, identification of the cause(s), and treatment of any specific pathology.[6] The underlying paradigm is to control pain so that rehabilitation can proceed. Rehabilitation should be individualized, and may include progressive exercises to promote flexibility, proprioception, strength, speed, agility and stability.

Much of the management of musculoskeletal injury has developed based on clinical experience with too little research evidence.[10,11] Consequently, there is a paucity of research evidence concerning acute musculoskeletal injury. Much of common practice is based on historical precedent rather than randomized controlled trials.[10] Indeed, it has been observed that even the most accepted treatments find little support when critically evaluated.

RICE

Rest, ice, compression, elevation (RICE) is a mnemonic used to guide the early treatment after acute musculoskeletal injury.[10] However, the evidence base for this intervention is lacking and guidance on how to apply ice and/or compression varies between sources. Thus, although widely accepted, there is little evidence for the effectiveness of this intervention, and even suggestion that it may be detrimental to recovery.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) can be used for analgesia and helping during recovery from acute musculoskeletal injury.[12] Topical NSAID gels can also be effective, as in addition to their therapeutic effects they are useful for self-massage.[12]

Conventional NSAIDs act by inhibiting cyclooxygenase (COX)-2 and the pathologic responses to pain and inflammation. In the gastrointestinal (GI) tract, they also inhibit COX-1 activity, decrease prostaglandins, and increase the risk of GI side effects such as life-threatening bleeding.[13] Conventional NSAIDs show dose-dependent side effects, which may limit their use in elderly people or other patients at high risk. Additional side effects include renal dysfunction and platelet inhibition.

The COX-2 specific agents (celecoxib) have a decreased incidence of GI toxicity, but increased costs and cardiovascular risks may limit their utility in the elderly and in those with cardiovascular risk factors. COX-2 selective agents (etodolac, meloxicam) have a decreased risk of clinically significant GI side effects compared with other NSAIDs, but the cardiovascular risks are unknown. Even with COX-2 specific or selective agents, GI protectivity may be compromised by concomitant use of even low-dose aspirin, and renal side effects are not decreased.

The Food and Drug Administration (FDA) issued a warning concerning the potential for elevation in liver function tests during treatment with all products (including topical formulations) containing diclofenac sodium. In post-marketing reports, cases of drug-induced hepatotoxicity have been reported in the first month but can occur at any time during treatment with diclofenac.[14]

NSAIDs are known to inhibit neutrophil aggregation and migration to sites of inflammation.[9] NSAIDs also alter neutrophil function in other ways such as the slowing of lysosomal enzyme release, decreased oxidative phosphorylation, and decreased production of substances that are chemotactic for other leukocytes. NSAIDs have also been shown to have anticoagulant effects by acting on platelets.

NSAIDs are also commonly used in the treatment of acute soft tissue injuries, yet their efficacy is not substantiated in the scientific literature. Indeed, there are suggestions that the short-term benefits of NSAIDs may be outweighed by long-term compromise of the structure and function of the injured tissue.[9] NSAID use can and does alter certain fundamental processes involved in the normal healing of injured tissues.[15] For example, experimental studies have documented the negative effects of NSAIDs on healing of skeletal tissues. Thus, the use of NSAIDs can profoundly affect skeletal health.

KEY FACT

While NSAIDs are often used to treat acute muculoskeletal injuries, their efficacy has not been substantiated in the scientific literature.

KEY FACT

Local corticosteroid injections have no role in the management of acute musculoskeletal injuries.

Corticosteroid injections

Local corticosteroids are used to reduce inflammation in patients with chronic tendinopathies, they have no role in the management of acute injuries.[5,6] Corticosteroid injections are one of the most commonly used treatments for chronic tendon lesions.[5] However, despite their popularity, the evidence for benefit is lacking and they have potential adverse effects. It is recognized that many of the recommendations for the use of local corticosteroid injections are based on anecdote, and there is no good evidence to support their use.[5]

When used to treat tendinopathy, corticosteroids can inhibit formation of adhesions, granulation, and connective tissue; reduce tendon mass; and decrease biomechanical integrity and the amount of load that can be taken before failure.[5] The biomechanical effects of peritendinous corticosteroid on human tendons are not established. However, case reports of rupture of tendons after injection are common.[5]

Intra-articular injection of corticosteroids is also a common treatment for osteoarthritis of the knee, see osteoarthritis section for more details.

Sepsis is reported in up to 1 in 17 intra-articular or soft-tissue injections.[5] Other commonly reported side effects include tissue atrophy, facial flushing, postinjection flare, and hypersensitivity reactions.

Traumeel®: a different approach

There is scope for improvement in the management of acute musculoskeletal injury. As much soft tissue pathology represents a failure to repair tissue adequately after injury, improving the wound-healing response seems an appropriate strategy for improving outcomes. Potential targets that have been proposed to achieve this include transforming growth factor beta (TGF-β), which may promote regeneration of the tendon matrix structure and composition.[6] Traumeel® has been shown to stimulate TGF-β production,[16,] and studies suggest that it has beneficial effects on the wound-healing process.[17]

The role of Traumeel® as a multi-component, multi-target preparation providing comprehensive treatment pathways in the complex inflammation cascade, using genomic approaches, is being further explored.

All of the formulations of Traumeel® contain 14 components. These are listed in Table 2, including the characteristics* of each ingredient.

Osteoarthritis

Osteoarthritis (OA), the most common form of joint disease, affects as much as 80% of the general population over the age of 75 years.[18] The degenerative joint changes that characterize this disorder are radiologically detectable and include subchondral bony sclerosis, synovitis, loss of articular cartilage, and osteophytes formed by proliferation of bone and cartilage in the joint.[19,20] In about 60% of sufferers these changes are accompanied by symptoms that include erythema, swelling and joint pain that often result in reports of morning stiffness, limitations in range of motion and restrictions in the activities of daily living.[21,22]

KEY FACT

Osteoarthritis can result in symptoms that include erythema, swelling and joint pain that often result in reports of morning stiffness, limitations in range of motion and restrictions in the activities of daily living.

The Framingham Osteoarthritis study demonstrated that radiographic evidence of OA increased with age, from 27% in patients younger than age 70, to 44% in patients age 80 or older. There was a slightly higher prevalence of radiographic changes of OA in women than in men (34% versus 31%); however, there was a significantly higher proportion of women with symptomatic disease (11% of all women versus 7% of all men; $p = 0.003$).[23] In a re-evaluation of the Framingham OA study, the authors concluded that in the elderly, new onset of knee OA is frequent and is more common in women than men. However, among the elderly, age may not affect new disease occurrence or progression.[24]

Pharmacological treatments for OA include analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular (IA) injections of steroids and IA injections of viscosupplementation of hyaluronic acid (HA).[25] Topical preparations, including capsaicin and NSAIDs, can also be used.[26] The supplements chondroitin sulfate and glucosamine are also commonly used by patients despite a lack of evidence for effectiveness.[27]

Guidelines recommend oral or topical NSAIDs for the initial management of osteoarthritis, and they are commonly used in practice.[26,28,29]

In a network analysis, comparison of the most commonly used pharmacologic interventions for knee OA–related pain at 3 months, the conclusions reached where that all treatments except acetaminophen showed clinically significant improvement in pain. The authors stated that IA treatments were more effective than oral NSAIDs for pain, which is possibly due to the contribution of the integrated IA placebo effect.[30]

Drawbacks of current treatments

Several retrospective analyses have concluded that non-selective NSAIDs pose an increased risk of gastrointestinal adverse events (AEs).[31–35] In general, these analyses have looked at patients undergoing long-term chronic therapy often with underlying inflammatory diseases such as OA.

Intra-articular injection of corticosteroids is also a common treatment for osteoarthritis of the knee, however, clinical evidence suggests that the benefit is short-lived, usually one to four weeks.[36] Additionally, concern has been expressed that long-term treatment could promote joint destruction and tissue atrophy.[36]

The data from clinical trials of viscosupplement products available in the public domain utilized heterogeneous methodologies and endpoints, and comparisons are therefore relatively difficult to interpret. These products appear to provide, at best, consistently moderate symptom improvement of OA knee pain despite the fact that viscosupplementation is universally used at a very significant cost. Improvements are often directional, and even when statistically significant, may not exhibit clinical endpoint effect sizes consistent with clinically relevant outcomes. Systematic reviews have provided confusing results. One concluded that IA HA has not been proven clinically effective and may be associated with a greater risk of AEs,[37] while a more recent network analysis comparing the relative efficacy of of treatments for knee OA concluded that IA HA was more effective than oral NSAIDs (except diclofenac), probably due to a beneficial effect of the IA procedure itself.[30]

KEY FACT

The effects of sub-clinical chronic inflammation in OA are now increasingly being recognized.

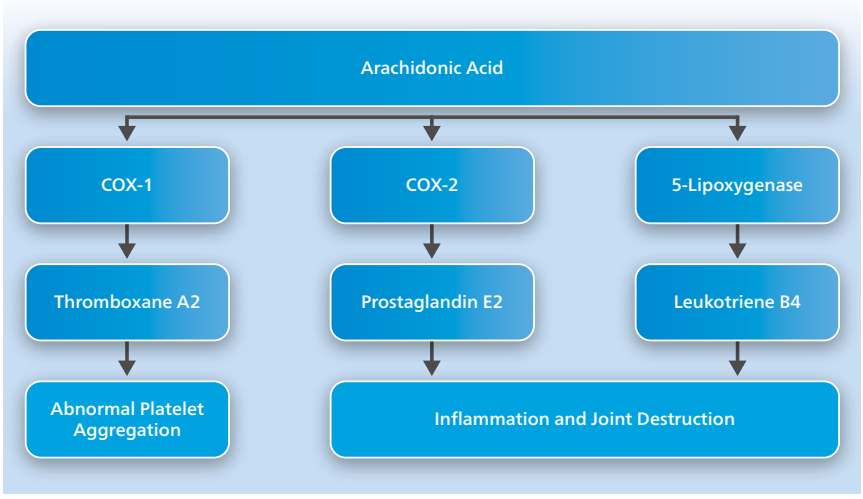
Role of inflammation

The effects of sub-clinical chronic inflammation in OA are now increasingly being recognized.[38] In the development of OA, the pro-inflammatory cytokines, IL-1, TNF-α·, IL-6 and other members of the IL-6 protein superfamily, such as IL-7, IL-17 and IL-18, have all been shown to be associated with cartilage damage and, therefore, the development of OA.[39–41] In contrast, chronic inflammation develops over a longer period of time and may persist for weeks, months or years. Markers of chronic inflammation, such as C-reactive protein (CRP), may be elevated in patients with OA, and may be mediated by IL-6, which is the major cytokine secreted by macrophages.[42] IL-6 may also play a role in angiogenesis, which is another factor contributing to the pathology of OA.[43,44]

Several enzymes, e.g., cyclo-oxygenase (COX) and lipoxygenase (LOX) – are catalysts for reactions, producing mediators of inflammation and pain. COX enzymes are responsible for the production of lipid mediators, including prostaglandins, prostacyclin and thromboxanes (Figure 1). There are two main isoforms of COX: COX-1 is expressed in most cells, and COX-2 is induced by pro-inflammatory agents (such as cytokines).[45] The majority of prostaglandin E2 (PGE2) is synthesized from arachidonic acid in cells by COX-2 enzymes and terminal prostaglandin E synthases.[46,47] PGE2 is a potent vasodilator, causing fluid to leak from blood vessels into the surrounding tissue and resulting in swelling. It is a principal mediator of inflammation and pain.[46,48]

LOX enzymes are responsible for the production of leukotrienes, which are lipid signalling molecules synthesized from arachidonic acid. An example is LTB4 which is synthesized by the 5-LOX enzyme. This is a powerful chemo-attractant for leukocytes (white blood cells),[49] and is implicated in the pathogenesis of inflammation.

Figure 1
Lipoxygenase (LOX) and cyclooxygenase (COX) enzymes synthesize mediators involved in inflammation and pain



Along with their roles in the pathogenesis of inflammation, the presence of inflammatory mediators, such as prostaglandins and leukotrienes, in the osteoarthritic joint lowers the threshold of pain, resulting in heightened pain sensations.[50]

Traditionally, non-steroidal anti-inflammatory drugs (NSAIDs) have been used to manage arthritic pain. They work by blocking the activity of COX enzymes. However, inhibition of COX enzymes by NSAIDs is associated with increased 5-LOX activity. Because they share the same substrate (arachidonic acid), inhibition of COX pathways results in increased substrate availability for 5-LOX, leading to a shift towards leukotriene production.[51] This increased leukotriene production has been implicated in the development of stomach ulcers,[52] as well as increased spasms of smooth muscles of airways and associated vasculature and therefore, increased risk of asthmatic attacks.[53,54]

Furthermore, leukotriene B4 (LTB4) in particular is elevated in chronic inflammatory joint diseases, such as rheumatoid arthritis, and has been implicated in the chronic inflammation and joint destruction associated with this disease.[54]

Zeel® T

Zeel® T works by modulating both the 5-lipoxygenase (5-LOX) and COX-1 and -2 pathways. For more information please refer to the Zeel® T product monograph.

Traumeel® and Zeel® T

Through their multicomponent and unique formulations, Traumeel® and Zeel® T address multiple targets and pathways that aim to regulate and support the inflammatory network and the microenvironment. The combination of Traumeel® and Zeel® T is a multi-ingredient, multi-target immunomodulation product that principally influences cytokines and TGF-β to attenuate cellular immunity while enhancing bone and cartilage formation.

KEY FACT

Together Traumeel® and Zeel® T address central aspects of knee OA to relieve pain and its underlying causes.

Together Traumeel® and Zeel® T address central aspects of knee OA to relieve pain and its underlying causes:

- Impaired inflammation (chronic inflammation of the articular and periarticular structures)[38]
- Angiogenesis (formation of new blood vessels)[38]
- Joint degradation (alteration in cartilage structure)[38]

The MOZArT study demonstrates that the intra-articular co-administration of Traumeel® /Zeel® T can reduce the pain associated with chronic moderate-to-severe knee osteoarthritis.[1]

For more information please refer to the monograph on Osteoarthritis of the Knee: a new effective treatment option with Traumeel® and Zeel® T injections.

3 Composition

Table 2
Traumeel® product absolute empiric composition and characteristics*.

Constituent	Characteristics*	Ointment/Gel per 100 g	Tablets per 300 mg	Ampoules for injection per 2.2 ml
Achillea millefolium *Milfoil*	Hemorrhages, especially precapillary arteriovenous (anastomosis), oozing hemorrhages	90 mg	0.015 mg	0.0022 µl
Aconitum napellus *Monkshood*	Fever with hot, dry skin, neuralgia, inflammatory rheumatism; improvement of the vasotonia; analgesic, hemostatic	5 mg	0.03 mg	0.0132 µl
Arnica montana *Mountain arnica*	To stimulate the healing of wounds, fractures, dislocations, contusions, hematomas, myocardial weakness, neuralgia, myalgia, analgesic, hemostatic	1.5 mg	0.15 mg	0.022 µl
Atropa belladonna *Deadly nightshade*	Localized reaction phases, cerebral sensitivity with cramp and delirium	5 mg	0.0075 mg	0.022 µl
Bellis perennis *Daisy*	Dislocations, contusions, sensation of soreness in the abdominal wall/cavity, exudative processes, resorption of edema	100 mg	0.06 mg	0.011 µl
Calendula officinalis *Calendula*	Slowly healing wounds, promotes granulation, analgesic	450 mg	0.15 mg	0.022 µl
Chamomilla *(Matricaria) recutita Chamomile*	Anti-inflammatory; stimulates granulation, promotes healing in difficulty healing wounds and ulcers; fistulae, hemorrhoids, mastitis, intertrigo, aphthous stomatitis, conditions of restlessness and excitation, disorders of dentition, otitis media, glandular swellings	150 mg	0.024 mg	0.0022 µl
Echinacea angustifolia *Narrow-leaved cone flower*	Increase in the mesenchymal defenses; inflammation of all kinds and locations; septic processes; hyaluronidase inhibiting, anti-inflammatory action	150 mg	0.06 mg	0.0055 µl
Echinacea purpurea *Purple cone flower*	Increase in the mesenchymal defenses; inflammation of all kinds and locations; septic processes; hyaluronidase inhibiting, anti-inflammatory action	150 mg	0.06 mg	0.0055 µl
Hamamelis virginiana *Witch hazel*	Venous stasis, varicose veins, (thrombo-) phlebitis, crural ulcers, hemorrhoids, venous hemorrhages, anti-inflammatory, analgesic	450 mg	0.15 mg	0.022 µl
Calcium sulfide Homeopathic name: *"Hepar sulfuris"*	Tendency to suppuration, especially on the skin and lymph glands (furuncles, pyodermia, panaritium, phlegmons), tonsillar abscesses, chalazions, hordeolums, hemicrania, urinary disorders, hypersensitivity to cold and draughts	0.000025 mg	0.0000003 mg	0.0000022 µl
Hypericum perforatum *St. John's wort*	Neural and cerebral injuries, e.g. commotio cerebri neural pains upon or after injuries hemostatic	0.00009 mg	0.03 mg	0.0066 µl
Mercuro-amidonitrate Homeopathic name: *"Mercurius solubilis Hahnemanni"*	Suppurations, abscesses, gingivitis, stomatitis, nasopharangeal catarrh, catarrh of the sinuses, cholangitis, shrinking action on edematous conditions	0.00004 mg	0.0000003 mg	0.0000011 µl
Symphytum officinale *Comfrey*	To accelerate callus formation in fractures periostitis, causalgia, disorders arising from amputation stumps contusions	0.01 mg	0.00000024 mg	0.0000022 µl

* Characteristics with reference to: Reckeweg H-H. Materia Medica – Homoeopathia Antihomotoxica". 4th edition. Baden-Baden: Aurelia Verlag, 2007.

Carrier substances

Ointment – Cetostearyl alcohol, paraffin, 13.8% alcohol
Gel – Carbomers, sodium hydroxide, 25% alcohol
Tablets – 6 mg lactose, 1.5 mg Mg-stearate
Ampoules for injection – 0.9% saline solution

In some countries the number of ingredients and their concentration may vary slightly. For country-specific product information, please contact your local Heel partner.

4 Mode of action

Therapeutic indications

Traumeel® is an effective treatment for acute processes of musculoskeletal disorders that involve inflammation, such as injuries or acute flare of chronic conditions. It is suitable for use in patients who require relief of symptoms associated with such injury.

It is indicated as a first-line treatment for patients with traumatic injuries of all kinds such as sprains, dislocations, contusions, hemarthrosis and effusions into a joint; regulation of inflammatory processes in various organs and tissues, including in particular acute and chronic/degenerative disorders of the musculoskeletal system.

KEY FACT

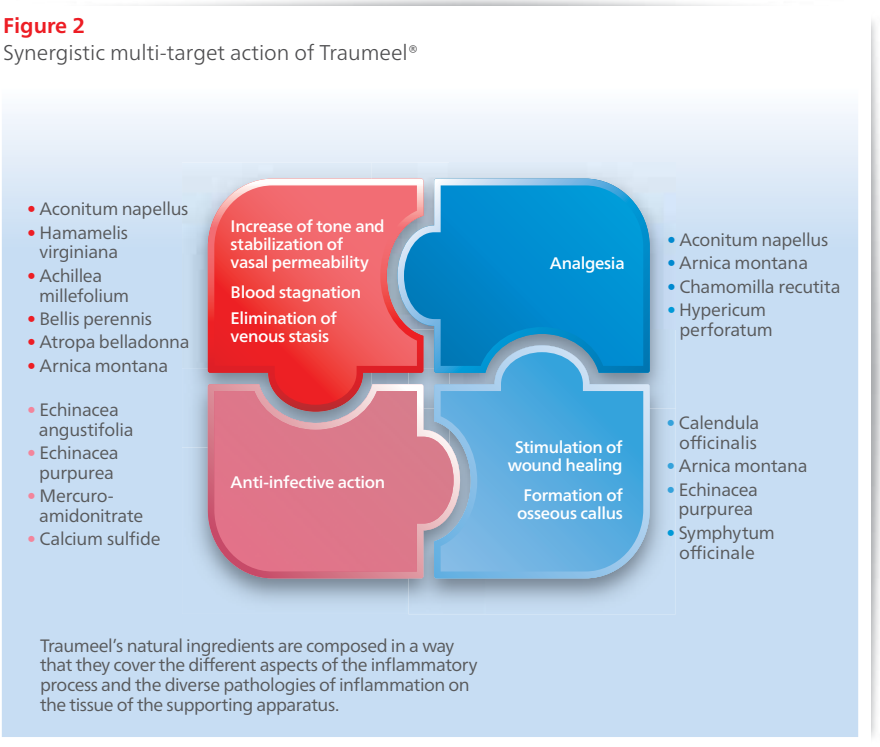
Traumeel® provides a multi-targeted, synergistic action to address multiple aspects of the inflammatory process and promote healing.

Synergistic multi-target action

The ingredients of Traumeel® are composed to cover the different aspects of the inflammatory phenomenon (Figure 2).

Multi-component medications, such as Traumeel®, are aimed at the modulation of both pro-inflammatory and anti-inflammatory pathways rather than suppression to restore and maintain homeostasis. As well as providing an anti-inflammatory action, the components of Traumeel® act to correct the effects of inflammation on body tissues. Thus, Traumeel® not only reduces inflammation, but it relieves pain and bruising and promotes healing after injury. This multi-target action prevents the vicious circle of reinforced tissue damage from activated inflammatory cells, modulating these cells toward tissue repair.

Figure 2
Synergistic multi-target action of Traumeel®



Traumeel's natural ingredients are composed in a way that they cover the different aspects of the inflammatory process and the diverse pathologies of inflammation on the tissue of the supporting apparatus.

KEY FACT

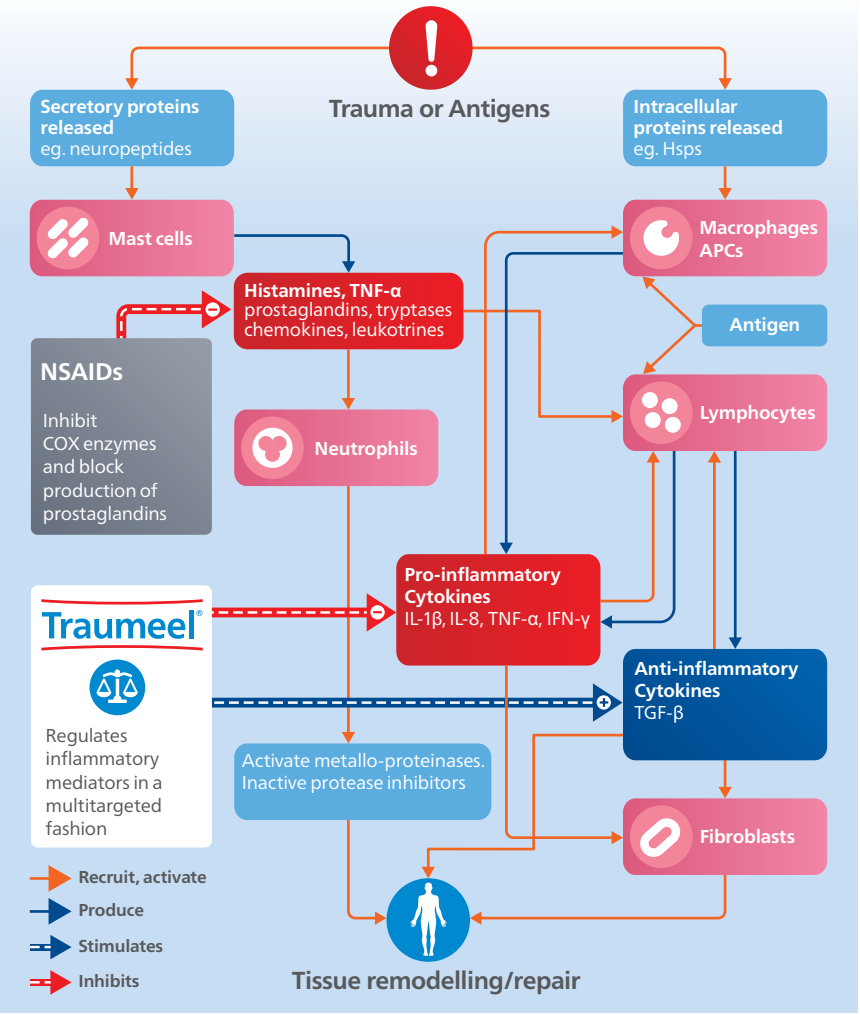
Traumeel® works differently from conventional anti-inflammatory drugs.

It has been suggested that Aconitum, Chamomilla, Hamamelis and Hypericum may reduce the pain associated with inflammation. Aconitum, Arnica, Hamamelis, Hypericum, and Millefolium may have anti-hemorrhagic effects. Arnica, Calendula, Symphytum and Echinacea may accelerate wound healing. Mercuro-amidonitrate may be an anti-inflammatory and anti-viral agent. Hamamelis may prevent the venous stasis. Calcium sulfide may improve cellular respiration.[17]

Pharmacodynamic properties

Traumeel® does not exert its therapeutic effects via the same mechanisms as conventional anti-inflammatory drugs.[55] Instead, it appears to interact with the fine and complex regulation of acute local inflammation.[55] While the precise mode of action of Traumeel® is not fully understood, *in vitro* and *in vivo* studies have shown that Traumeel® may exert an effect on regulatory pro-inflammatory and anti-inflammatory mediators (Figure 3).[16,56]

Figure 3
The observed effects of Traumeel® on mediators of inflammation.[16,56]



In vitro studies

Transforming growth factor beta (TGF-β) has been established as a mediator that inhibits immune-system cells. Thus, the local production of TGF-β by regulatory T cells can prevent other pro-inflammatory lymphocytes from continuing to support the actual inflammatory reaction.[16]

In vitro studies utilizing whole blood cultures to more closely approximate conditions *in vivo*, have shown that low-potency plant extracts, such as those used in Traumeel®, are capable of stimulating production of the inhibitory cytokine TGF-β.[16]

Traumeel® has been shown to have an effect on the secretion of the pro-inflammatory cytokines tumor necrosis factor alpha (TNF-α) and interleukin (IL)-1β, and chemokine IL-8.[56] *In vitro*, Traumeel® has been shown to reduce secretion of:[56]

- IL-1β by up to 70% in both resting and activated T cells and monocytes ($p<0.05$)
- IL-1β by up to 50% in resting human gut epithelial cells and 80% in TNF-α- activated gut epithelial cells ($p<0.01$)
- TNF-α by up to 65% in resting T cells and monocytes, and up to 54% in activated T cells and monocytes ($p<0.01$)
- IL-8 by up to 50% in both resting and activated monocytes ($p<0.05$).

Conversely, Traumeel® did not increase the secretion of these pro-inflammatory mediators, whether or not the cells were activated by other means, suggesting that Traumeel® lacks any activating (or pro-inflammatory) capacity.[56] These results support the characterization of Traumeel® as an anti-inflammatory medication.[56]

In addition, *in vitro* studies have shown that Traumeel®, at the highest concentration attainable in connective tissues by local injection, is not toxic to leukocytes and platelets. Thus, the normal defensive and homeostatic functions of these cells are preserved (see Clinical safety, page 56).[55]

KEY FACT

Traumeel® has been shown to reduce the secretion of pro-inflammatory cytokines and chemokines *in vitro*.

KEY FACT

Animal studies indicate that **Traumeel®** acts to speed up the healing process rather than blocking the development of edema.

Pre-clinical studies

In pre-clinical investigations,Traumeel® showed a broad range of anti-inflammatory and immunomodulatory effects *in vitro* and *in vivo*. Wound healing and antioxidative effects were also demonstrated in animal models. *In vivo* assessment of Traumeel® in acute inflammation has utilized the carrageenan-induced edema test in rats.[55] The carrageenan-induced edema test involves injecting a rat paw with carrageenan, which induces edematous swelling, and measuring the degree of increase in paw volume in the presence or absence of Traumeel® (saline was used as a control). A significant reduction in edema volume of up to 15% was observed when Traumeel® was injected an hour before carrageenan ($p=0.05$). This level of inhibition is similar to the effect exerted by aspirin at a dose of 30 mg/kg in the same experimental model.

Traumeel® has also been investigated in chronic inflammation using an adjuvant arthritis model in rats.[55] The therapeutic administration of Traumeel® led to a significant reduction in acute local inflammation (first phase of adjuvant arthritis) in comparison with the controls. However, Traumeel® did not appear to modulate the arthritic process, instead the effects of Traumeel® were limited to a symptomatic action on local inflammation.

Further investigation utilized an intra-paw injection of a small amount of homologous blood to model a traumatic blood extravasation in rats.[17] The effect of Traumeel® on edema development following local blood injection was found to document a time-dependent edema reduction. During the first hour, increase in paw volume was identical between Traumeel®and controls, however, during the second hour Traumeel®-treated paws decreased in volume while control-treated paws increased in volume with a peak at 2 hours. At 3 and 5 hours post blood injection, local inflammation was significantly lower in rats treated with Traumeel® compared with controls ($p<0.05$ at 3 hours and $p<0.01$ at 5 hours).

Interestingly, when only the components of Traumeel® that demonstrated individual edema inhibition were injected, the effect was lower than that of the complete Traumeel® formulation suggesting a synergistic effect of the other components.[17] Also, when levels of IL-6, a pro-inflammatory cytokine, were examined at 5 hours post blood injection, levels were significantly reduced by 45% in Traumeel®-treated rats compared with controls.

"The effect of Traumeel® is higher than the 'sum' of its active constituents."[17]

KEY FACT

The components of **Traumeel®** act synergistically to accelerate the healing process.

Summary

Multi-component medications, such as Traumeel®, are aimed at the modulation of both pro-inflammatory and anti-inflammatory pathways to restore and maintain homeostasis rather than suppressing them. It can be concluded that Traumeel® seems to act by speeding up the healing process instead of blocking the development of edema from the beginning. Thus, it appears that Traumeel® accelerates the tissue changes involved both in the formation and in the elimination of edema, with a net beneficial effect.[17]

While the precise mode of action of Traumeel® has yet to be fully elucidated, it appears likely that it has complex interactions with the cytokine network, which regulates inflammatory responses. Studies have shown that Traumeel® reduces concentrations of pro-inflammatory mediators, including TNF-α, IL-1β, IL-6 and IL-8, as well as an increase in TGF-β secretion probably via an increase in regulatory T cell expression.

It is also apparent that the effect of Traumeel® is not mediated by any one action of its individual constituents. Rather the components of Traumeel® act synergistically to accelerate the healing process. Thus, further work is needed to detail the multifaceted actions of Traumeel® on the complex network of cytokines regulating the inflammatory process.

Relationship between concentration and activity

The formulations of Traumeel® use low concentrations of a mixture of active ingredients making conventional pharmacokinetic parameters difficult to establish. It is thought that the activity of Traumeel® can be partly explained by the concept of hormesis.

Hormesis is a dose–response phenomenon characterized by a U-shaped dose–response curve.[57] Hormesis characterizes the dose–response continuum as stimulatory at low and ultra-low doses and inhibitory at high doses, leading to the biphasic, hormetic dose–response curve.

KEY FACT

The activity of **Traumeel®** can be explained by the concept of hormesis: a dose-response phenomenon characterized by a U-shaped dose-response curve.

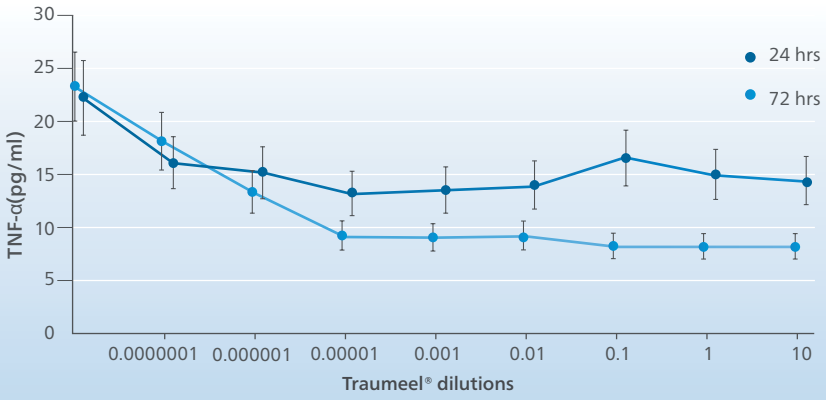
Hormesis may be explained as a response to a disruption in homeostasis. At low levels of disruption or toxicity many biological systems display an overcompensation response, which results in the apparent low-dose stimulation component of the response curve. At higher doses, the system often displays a more limited capacity for a compensatory response, usually insufficient to return to control values.[57]

A number of pharmacologically based receptor systems that affect a broad range of crucial physiological and behavioral responses have been shown to display biphasic responses. These include receptor systems known to be involved in inflammatory pathways including bradykinin, nitric oxide, prostaglandin, TGF-β and TNF-α.[57] In many instances, pharmacological systems have evolved highly efficient biological regulatory strategies in which the same endogenous agonist can elicit a stimulatory or inhibitory response depending on its concentration.

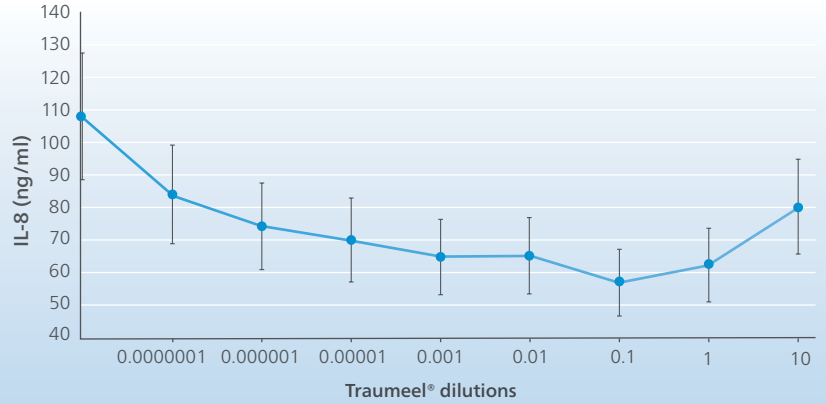
In vitro studies of the effects of Traumeel® on human leukocyte function have demonstrated an inverse dose response curve at dilutions of 10-1 – 10-7 that is consistent with a hormetic dose–response curve.[56] Using human leukocytes and gut epithelial cells to investigate the secretion of the pro-inflammatory cytokines IL-1β and TNF-α, and the chemokine IL-8 in response to Traumeel® exposure at different concentrations, *Porozov et al* found that Traumeel® had an inhibitory effect in a unique dose-dependent fashion (Figure 4, page 25).[56]

Therefore, it is thought that the optimal anti-inflammatory effect of Traumeel® requires exact concentrations of the active compounds. At dilutions that are too high or too low, Traumeel® would fail to exert an inhibitory effect on cytokine secretion.

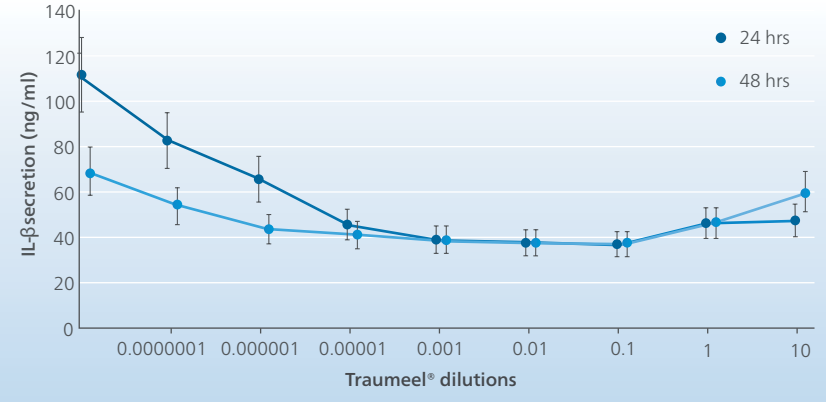
Figure 4
Effects of varying Traumeel® concentration on secretion of TNF-α (top), IL-8 (middle), and IL-1β (bottom). Each data point represents the mean (±SD) of triplicate ELISA wells.[56]



THP-1 and Jurkat cells were maintained under tissue culture conditions while exposed to serial dilutions of Traumeel® for 24 hrs and 72 hrs.



Cells from the human gut epithelial cell line, HT-29, were incubated (24 hrs) with the indicated concentrations of Traumeel and IL-8 secretion was measured using ELISA.



HT-29 cells were exposed to Traumeel for 24 hrs or 48 hrs prior to the measurement of IL-1β secretion.

KEY FACT

It is thought that exact concentrations of the active compounds are required to achieve the optimal anti-inflammatory effect of **Traumeel®**

5 Clinical studies

Randomized controlled clinical trials

Topical Traumeel® vs. diclofenac gel: Treatment of acute sprains of the ankle: TAASS

Reference: González de Vega C, Speed C, Wolfarth B, González J. Traumeel vs. diclofenac for reducing pain and improving ankle mobility after acute ankle sprain: A multicentre, randomized, blinded, controlled and non-inferiority trial. *Int J Clin Pract* 2013;67(10): 979–989. Doi: 10.1111/ijcp.12219.

Study design:	Randomized, controlled, blinded study.
Formulation:	Traumeel® ointment and gel.
Indication(s):	Unilateral sprain of the lateral ligaments of the ankle joint (grades 1 and 2).

Study design

- 449 physically active patients aged 18–40 years with unilateral sprain of the lateral ligaments of the ankle joint (grades 1 and 2).
- Blinded* randomization to:
  - 2 g Traumeel® ointment (n=152).
  - 2 g Traumeel® gel (n=150).
  - 2 g diclofenac 1% gel (n=147).
- Treatment administered topically three times a day for 14 days.
- Follow-up was over 6 weeks.

End points

- Primary end points:
  - Ankle pain assessed by patients on a 0–100 mm Visual Analogue Scale (VAS) on day 7.
  - The Activities of Daily Living (ADL, 0–100) subscale of the Foot and Ankle Ability Measurement (FAAM)** on day 7.
- Secondary end points measures at other time points 4,7, 14 and 42 included:
  - Ankle pain assessed by patients on a 0–100 mm Visual Analogue Scale (VAS).
  - The Activities of Daily Living (ADL, 0–100) subscale of the Foot and Ankle Ability Measurement (FAAM).
  - Swelling measured using the 'figure-of-eight' method calculating the mean of three repeated measurements.
  - Global efficacy assessment, participant assessed on a 5-point rating scale (1 = very good, 5 = worsening of symptoms) at day 14.
  - Time to return to normal activity (training and sports) assessed on day 42.

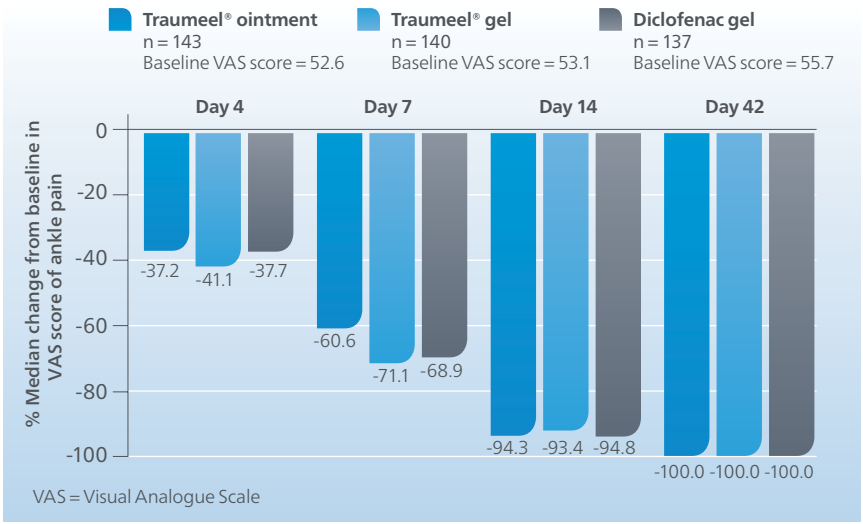
* Double-blind (investigator and subject) for Traumeel® gel and diclofenac gel, and single-blind for Traumeel® ointment (investigator blinded; drug in preparation unknown to subject).

** The FAAM is a validated self-reported questionnaire [Martin 2005) that assesses physical function of individuals with musculoskeletal disorders of the leg, foot, and ankle. The FAAM ADL consists of 21 single items assessing activities of daily living such as standing, walking, and going up and down stairs

Results

- On day 7, median percentage reductions in VAS pain score were demonstrated by all groups (Figure 5).
- Traumeel® ointment 60.6% (median: baseline 52.6 mm; change -33.0 mm).
- Traumeel® gel 71.7% (median: baseline 53.1 mm; change -37.1 mm).
- diclofenac gel 68.9 % (median: baseline 52.6 mm; change -37.1 mm).
  - Total pain relief was reported by 8.5%, 5.0% and 5.9% of patients in Traumeel® ointment, Traumeel® gel and diclofenac groups, respectively.
- On day 14, median percentage reductions in VAS pain score were 94.3%, 93.4% and 94.8% for Traumeel® ointment, Traumeel® gel and diclofenac groups, respectively (median changes: -46.4, -50.5 and -50.5 mm).

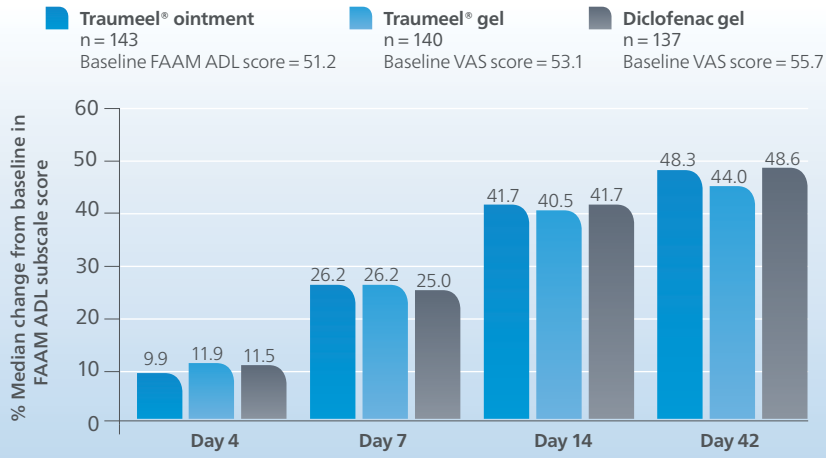
Figure 5
Median percentage change in VAS pain scores from baseline.



VAS = Visual Analogue Scale

- On day 7, median improvements in FAAM ADL score were 26.2, 26.2 and 25.0 points for Traumeel® ointment, Traumeel® gel and diclofenac groups, respectively (median baseline: 51.2, 56.0 and 51.2 points) (Figure 6).
- On day 14, median improvements in FAAM ADL score were 41.7, 40.5 and 41.7 points for Traumeel® ointment, Traumeel® gel and diclofenac groups, respectively.

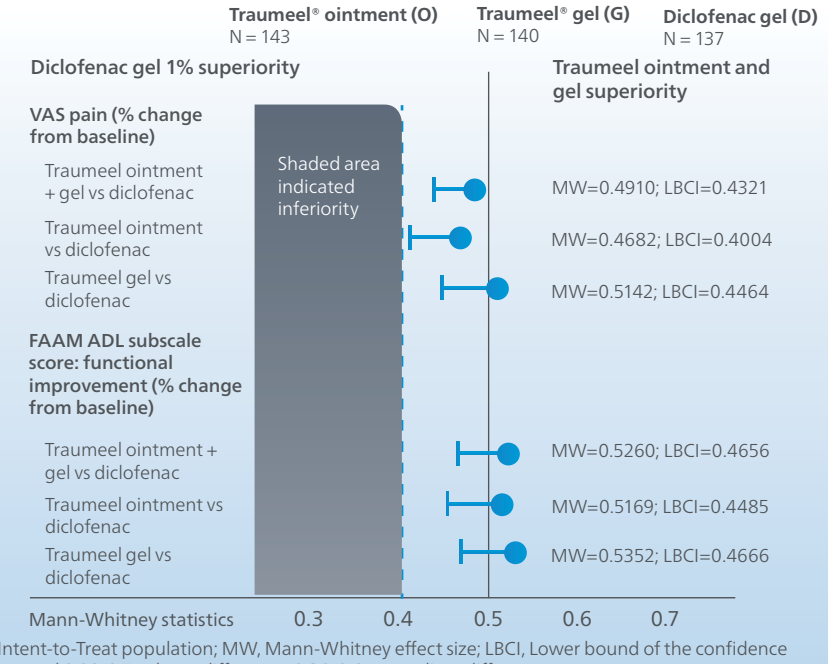
Figure 6
Median change from baseline in FAAM ADL subscale score.



FAAM = Foot and Ankle Ability Measurement;
ADL = Activities of Daily Living

- An overview of the primary endpoint results, day 7, is shown in Figure 7.
- Confidence intervals were above the predefined lower equivalence margin (0.40), demonstrating that Traumeel® ointment and gel are non-inferior to diclofenac gel 1%.

Figure 7
Traumeel® (ointment and gel) is non-inferior to diclofenac gel 1% in reducing pain and improving function (day 7).



Intent-to-Treat population; MW, Mann-Whitney effect size; LBCI, Lower bound of the confidence interval 0.29/0.71= large difference; 0.36/0.64 = medium difference; 0.44/0.56 = small difference; 0.5 = equality

- Traumeel® ointment and gel were non-inferior to diclofenac for all secondary outcome variables (Table 3).
  - Median reductions in ankle swelling were demonstrated by all groups on days 4, 7 and 14.
  - On day 14, median reduction in ankle swelling was –0.67, –0.67 and –0.57 for Traumeel® ointment, Traumeel® gel and diclofenac, respectively.
  - Global assessment of treatment efficacy was similar between treatment groups.
  - On day 14, over 92% of participants rated their treatment as 'very good' or 'good' in all treatment groups.

Table 3
Secondary efficacy variables

	Traumeel® Ointment/Gel N = 143	Traumeel® Ointment/Gel N = 140	Traumeel® Diclofenac gel N = 137
Ankle pain (VAS) score, median			
Change from baseline (day 14), %	-94.3	-93.4	-94.8
Baseline	52.6	53.1	55.7
Absolute score (day 14)	3.1	4.1	3.1
FAAM ADL subscale score, median points			
Change from baseline (day 14)	41.7	40.5	41.7
Baseline	51.2	56.0	51.2
FAAM Sports subscale score, median points			
Change from baseline (day 14)	50.0	50.0	50.0
Baseline	18.8	25.0	18.8
Ankle swelling, 'figure of eight', median, cm			
Change from baseline (day 14)	-0.67	-0.67	-0.57
Baseline	55.13	54.07	54.00
Normal function/activity, participants reporting scores of 0 or 1 n (%)			
Day 14	128 (89.5%)	133 (95.0%)	131 (95.6%)
Baseline	29 (20.3%)	23 (16.4%)	27 (19.7%)
Global assessment of treatment efficacy[a]			
Day 14, mean	1.6	1.6	1.5
No. (%) participants reporting treatment as "very good"/"good"	131 (92.3%)	128 (92.1%)	127 (92.7%)
Rescue medication (paracetamol)			
No. (%) participants (treatment/follow up periods)	28 (19.7%)	29 (20.7%)	20 (14.6%)
Tablets per participant, mean	1.5	1.6	1.0

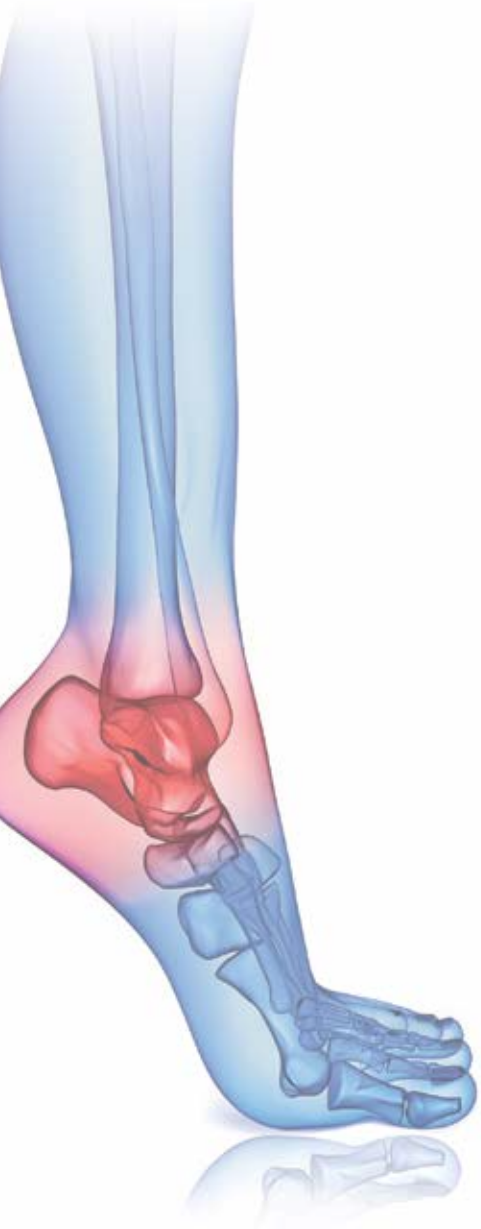
Negative figures indicate a reduction

[a]Participant assessed on a 5-point rating scale (1=very good, 2=good, 3=satisfactory, 4=no improvement, 5=worsening of symptoms)

- At 6 weeks, all patients reported total pain relief and normal functioning.
  - Median time to return to normal activity was 19.09, 19.35 and 19.39 days for Traumeel® ointment, Traumeel® gel and diclofenac groups, respectively.
- Adverse events (n=43) were reported by 31/447 patients (6.9%).
  - Events were mostly mild or moderate in severity, none was serious and all treatments were equally well tolerated.

Conclusions

- In this large-scale trial, Traumeel® ointment and gel decreased pain and improved joint function to the same extent as diclofenac 1% gel in acute ankle sprain.
- All treatments demonstrated a good tolerability profile.
- Traumeel® can be considered an effective first-line local treatment option and an alternative to topical diclofenac 1% gel for treating acute ankle sprain.



Topical Traumeel® vs. Placebo: Treatment of acute sprains of the ankle

Reference: Zell J, Connert WD, Mau J, Feuerstake G. Behandlung von akuten Sprunggelenksdistorsionen: Doppelblindstudie zum Wirksamkeitsnachweis eines homöopathischen Salbenpräparats. Fortschr Med 1988;106(5):96–100. English translation available in *Biol Ther.**

Study design: Randomized, placebo-controlled double-blind study.
Formulation: Traumeel® ointment.
Indication(s): Activity-related ankle sprains.

Study design

- Patients with distortion of the articular-capsule ligaments (sprain) and of the tendons of the ankle were randomized to:
  - Traumeel® n=33: 25 male, 8 female; mean age 23; mean time from injury 10.8 hours.
  - placebo n=36: 25 male, 11 female; mean age 22; mean time from injury 10.5 hours.
- Treatment was administered on an out-patient basis for 2 weeks – patients visited clinic on days 1, 3, 5, 8, 10, 12 and 15.
  - Both therapist and patients were blinded to medication.
  - All patients received electrotherapy as basic treatment.
  - Approximately 10–12 g of either Traumeel® or vehicle (placebo) was administered by applying a compression ointment bandage.

End points

- Primary end point: a pilot study identified the difference in total angulation of the joint – measured in extension and flexion between affected and non-affected joints – as a quantifiable objective measure for the degree of improvement in ankle mobility.
- Secondary end points:
  - the inversion angle (supination).
  - the degree of pain suffered upon movement measured on a 3-point scale with the score values of: 0=no pain; 1=mild pain; 2=severe pain.

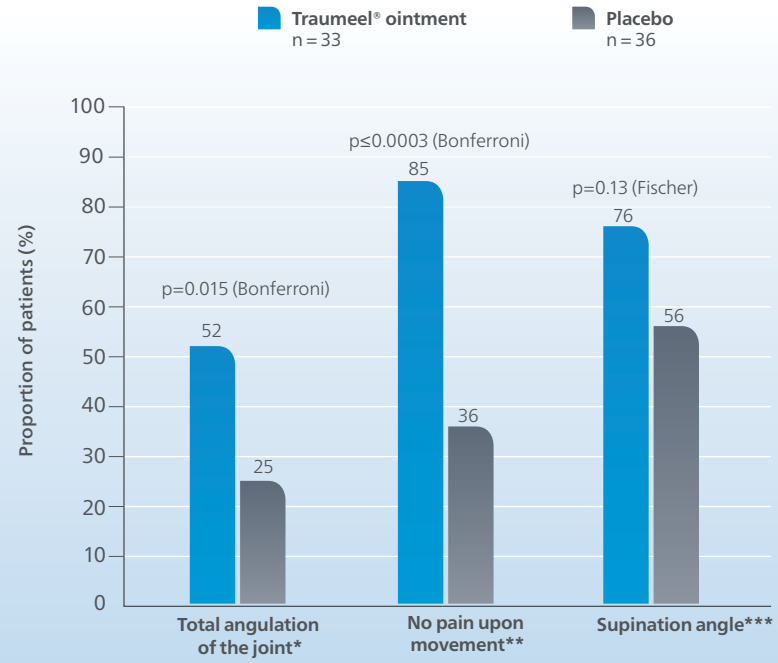
Results

- In both groups, the basic treatment produced an improvement in joint mobility. At day 10, the difference in total angulation of the joint between affected and non-affected joints was significantly less in Traumeel®-treated patients compared with placebo (p=0.015) (Figure 8).
- Treatment was defined as successful if the difference in the angular sums between injured and non-injured ankles decreased to ≤10 by day 10. The probability of successful treatment was significantly greater with Traumeel® than placebo (p=0.03).

* Zell J, Connert WD, Mau J, Feuerstake G. Treatment of acute sprains of the ankle: a controlled doubleblind trial to test the effectiveness of a homeopathic ointment. *Biol Ther* 1989;VII(1):1–6.

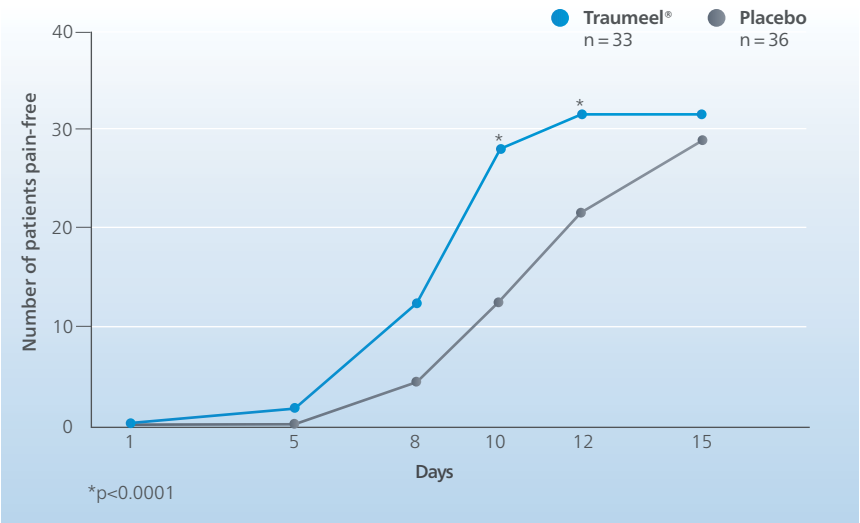
- A significantly greater proportion of Traumeel® patients had no pain upon movement on day 10 compared with placebo patients (p≤0.0003) (Figures 8 and 9).
- While more patients receiving Traumeel® than placebo achieved a difference in supination angle between injured and non-injured ankles of ≤7 at day 10, this did not achieve significance (p=0.13) (Figure 9).

Figure 8
Proportion of patients achieving "success" in the different end points



* Difference of the angular sums of flexion + extension between injured and healthy ankles decreased to 10 or less after 10 days of treatment.
** No longer pain upon movement after 10 days of treatment.
*** Difference of the supination angle between the injured and non-injured ankles decreased to 7 or less after 10 days of treatment.

Figure 9
Patients with no pain upon movement within two weeks after beginning therapy with Traumeel® ointment.



Conclusions

- Traumeel® is effective in the treatment of activity-related sprains of the ankle.
- Traumeel® improved ankle mobility and pain significantly.

Topical Traumeel® vs. Placebo: Treatment of acute musculoskeletal injuries

Reference: Böhmer D, Ambrus P. Treatment of sports injuries with Traumeel® ointment: a controlled double-blind study. *Biol Ther* 1992;X(4):290–300.

Study design: Randomized, placebo-controlled, double-blind study.
Formulation: Traumeel® ointment.
Indication(s): Acute musculoskeletal injuries.

Study design

- Patients with visible or palpable alteration in tissue, with injury as a consequence of sprain or contusion of a slight or moderate degree of severity, were randomized to receive:
  - Traumeel® n=34: 21 male, 13 female; mean age 31; 20 contusions, 14 sprains.
  - placebo n=34: 23 male, 11 female; mean age 30; 11 contusions, 23 sprains.
- Patients received their first medication no later than on the fourth day after the injury (no other medication was given between injury and beginning of treatment).
- Following initial treatment, the patients applied 6–10 g of either Traumeel® or placebo ointment twice daily themselves, until day 15. An occlusive bandage was applied over the ointment for 30 minutes and the dressing covered with a cold compress while the injured extremity was rested.

End points

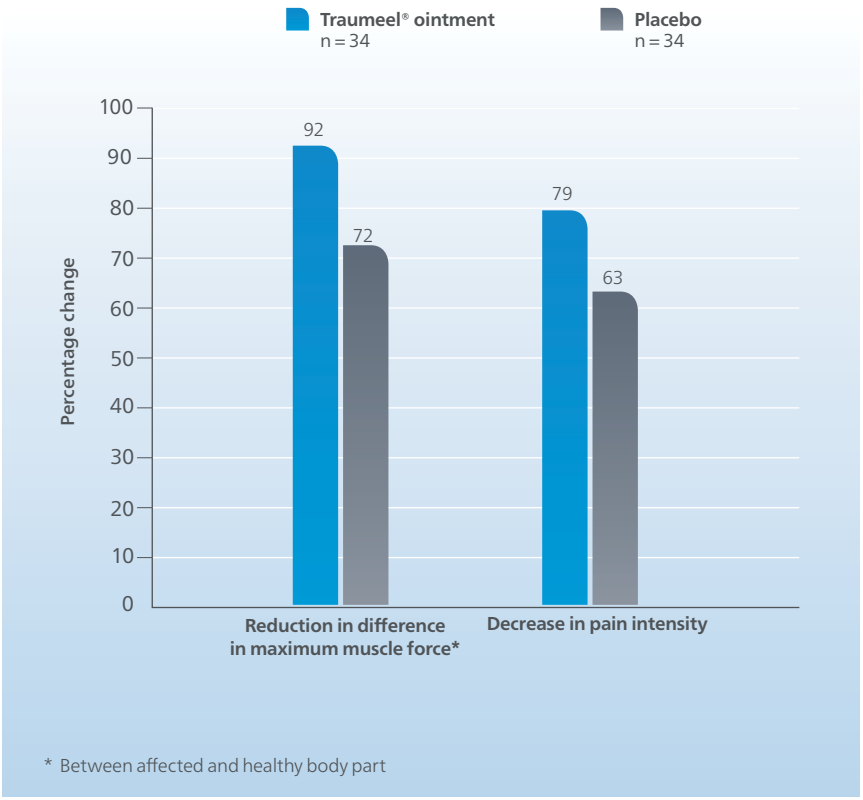
- Primary end point: abatement of swelling assessed by measured circumference.
- Secondary end points:
  - maximum muscle force (difference between the injured body part andthe contralateral uninjured side).
  - pain intensity measured on a 3-point scale (0=no pain, 1=slight pain, 2=severe pain) and summed for: at rest, in motion, and under pressure (range 0–6).
  - time until resumption of normal activity.
  - overall evaluation of effectiveness by patient and physician (very good, good, moderate, poor).

Results

- Swelling decreased more in the Traumeel® group than in the placebo group.
- By day 15, improvement in maximum muscle force was greater in the group receiving Traumeel® versus placebo (92% improvement versus 72%, see Figure 10).
- By day 15, pain was reduced by nearly 80% in the Traumeel® group and 63% in the placebo group ($p<0.001$) (Figure 10).

- Normal activities were resumed earlier in patients receiving Traumeel® compared with placebo (mean 12.1 days versus 13.5 days, respectively).
- Treatment with Traumeel® was assessed as "very good" or "good" by 85% of patients and 74% of physicians, compared with 50% and 35% for placebo treatment, respectively. In no case was treatment with Traumeel® assessed as poor compared with 35% of physician's assessments of placebo.
- At the end of the study, all patients and physicians evaluated the tolerance of both Traumeel® and placebo either as "good" or "very good".
- No undesired side effects were observed during the course of the study.

Figure 10
Changes in maximum muscle force and decrease in pain after 15 days of treatment in %



Conclusion

Traumeel® is significantly more effective than placebo in the treatment of acute musculoskeletal injuries.

Topical Traumeel® vs. Placebo: The treatment of traumatic blood effusions of the knee joint

Reference: Thiel W, Borho B. Posttraumatische Kniegelenksergüsse und intraartikuläre Traumeel-N-Injektion. *Orthopädische Praxis* 1991;11:721–725. English translation available in *Biol Ther.**

Study design: Randomized, placebo-controlled double-blind trial.
Formulation: Traumeel® injection.**
Indication(s): Hemarthrosis of the knee.

Study design

- Patients with acute, post-traumatic irritation of the knee joint with hemarthrosis (10–50 ml effusion) were randomized to receive:
  - Traumeel® n=37: 24 male, 13 female; mean age 36 years.
  - physiological saline solution n=36; 24 male, 12 female; mean age 36 years.
- All patients were given an intra-articular injection on days 1, 4 and 8 with 2 ml injection solution after which a support dressing was applied. The observation period for each patient was 36 days.

End points

- Extent of swelling by measuring circumference of knee joint.
- Mobility of injured and healthy joints.
- Pain at rest, on movement and under pressure measured using 3-point scale (0=none, 1=slight, 2=severe).
- Volume and nature of puncture fluid.

Results

- After a single injection, only 13.5% of the patients in the Traumeel® group required further punctures, compared with 25% in the placebo group.
- On the 8th day after the start of treatment, the punctuate was still bloody in 5.4% of the Traumeel® group vs. 19.4% of the placebo group.
- Degree of movement was improved on day 8: 82.8% with Traumeel® vs. 56% with placebo.
- Swelling was reduced by 73.2% in the Traumeel® group and 51.3% in the placebo group.
- Success of treatment by day 8 is shown in Figure 11.
- Greater reductions in pain were seen in the Traumeel® group compared with the placebo group through day 8 (Figure 12).

* Thiel W, Borho B. The treatment of recent traumatic blood effusions of the knee joint. *Biol Ther* 1994;XII(4):242–248.

** The formulation used in this study was the same as the standard Traumeel® formulation with one additional ingredient.

- By day 36, 95% of Traumeel® patients questioned had resumed normal activities compared with only 58% of placebo patients.
- In all patients, treatment was tolerated without side effects or complications.

Figure 11
Success of treatment by day 8 (maximum difference in circumference of joint 0.5 cm and maximum difference in mobility 10 degrees between healthy and injured joints).

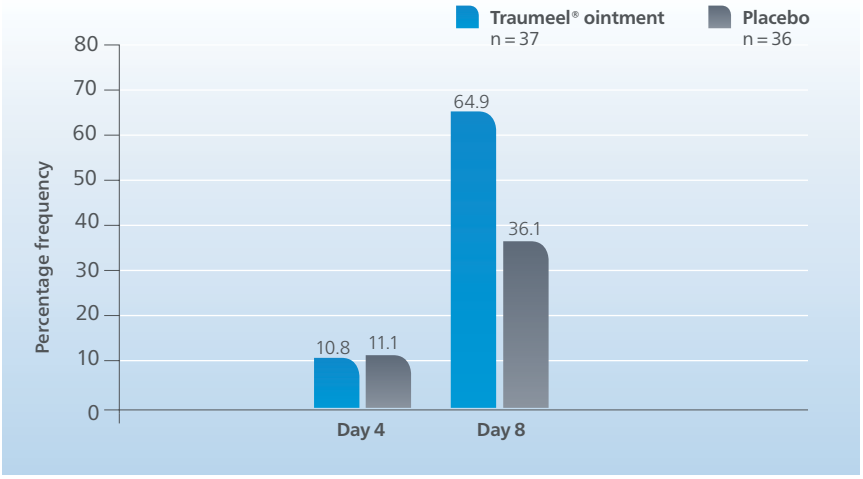
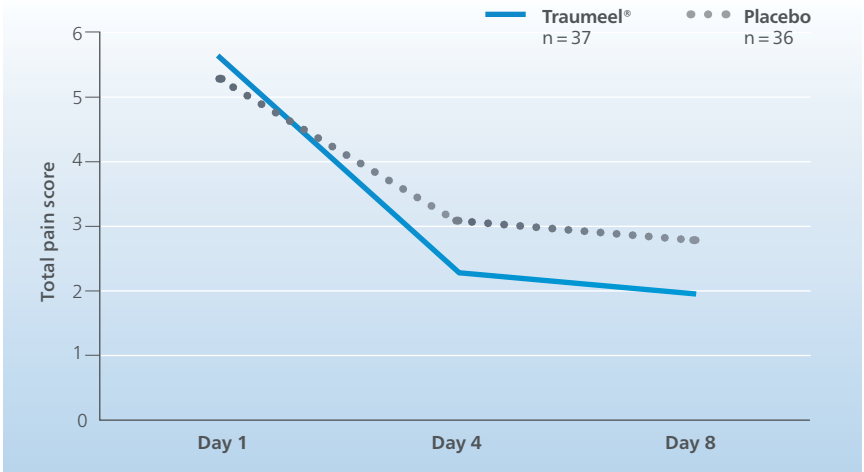


Figure 12
Mean values for total pain score on days 1, 4 and 8.



Conclusion

This study shows that intra-articular injection therapy with Traumeel® produces fast regression of blood effusions of the knee.

Note: The therapeutic process for treating recent traumatic blood effusions of the knee joint not involving any ligament or cartilage bone structures involves effusion (the escape of fluid) punctures in the area under sterile conditions to drain the hemarthrosis. During the puncture process, the joint may also be flushed using a neutral liquid, such as physiological saline solution, and this is usually followed by an intra-articular injection of an anti-inflammatory agent.

Traumeel® in co-administration with Zeel® T (intra-articular injections) for the treatment of knee osteoarthritis: the MOZArT study

Reference: Lozada C, del Rio E, Reitberg D et al. A multi-center double-blind, randomized, controlled trial (db-RCT) to evaluate the effectiveness and safety of co-administered Traumeel® (Tr14) and Zeel® (Ze14) intra-articular (IA) injections versus IA placebo in patients with moderate-to-severe pain associated with OA of the knee. *Arthritis Rheumatol* 2014; 66(suppl):S1266. Abstract no. 2896.

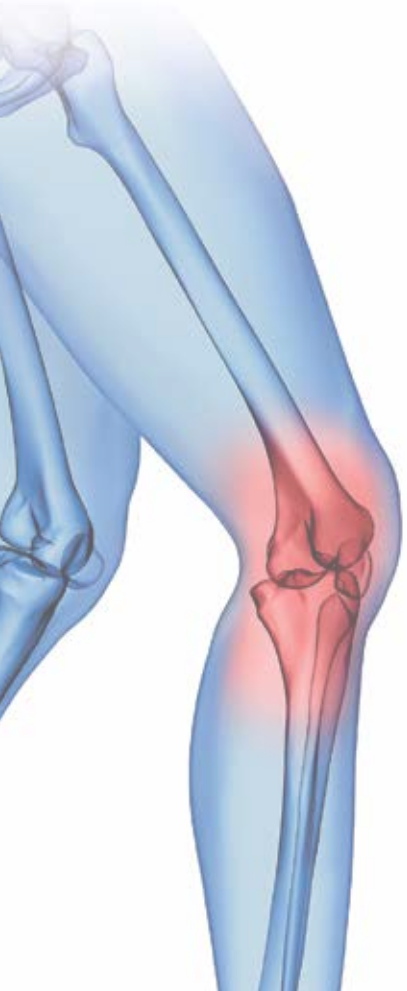
Study design:	Multi-center, randomized, placebo-controlled double-blind trial.
Formulation:	Traumeel® injection combined with Zeel® T injection.
Indication(s):	Moderate-to severe chronic knee osteoarthritis.

Study design

- Patients with moderate-to-severe chronic knee OA were randomized to receive 3 weekly intra-articular injections of:
  - Traumeel® and Zeel® T n=119
  - saline solution n=113.
- The study lasted 17 weeks (screening, wash-out, lead-in, treatment period and follow-up period).

End points

- Primary endpoint
  - Change in knee pain from Baseline to End-of-Study (Week 17) as measured by the WOMAC* OA Pain Subscale (Section A, 1–5) 100 mm VAS
- Secondary endpoints
  - Total WOMAC and sub scores for stiffness (B), and physical function (C)
  - Change in pain following a 50 ft walk (100 mm VAS)
  - Consumption of rescue medication
  - Patient and physician global assessments.
- Clinical relevance was assessed by comparing proportions of patients with reductions from baseline in WOMAC A scores greater than a validated benchmark Minimal Clinically Important Difference (MCID). This was chosen as -32.6 mm (the most conservative value) based on a study of outpatients with knee or hip OA where WOMAC VAS MCIDs ranged from -7.9mm to -32.6mm.[58]
- Safety was assessed by monitoring of vital signs, physical examinations of the target knee, adverse events and concomitant medications.

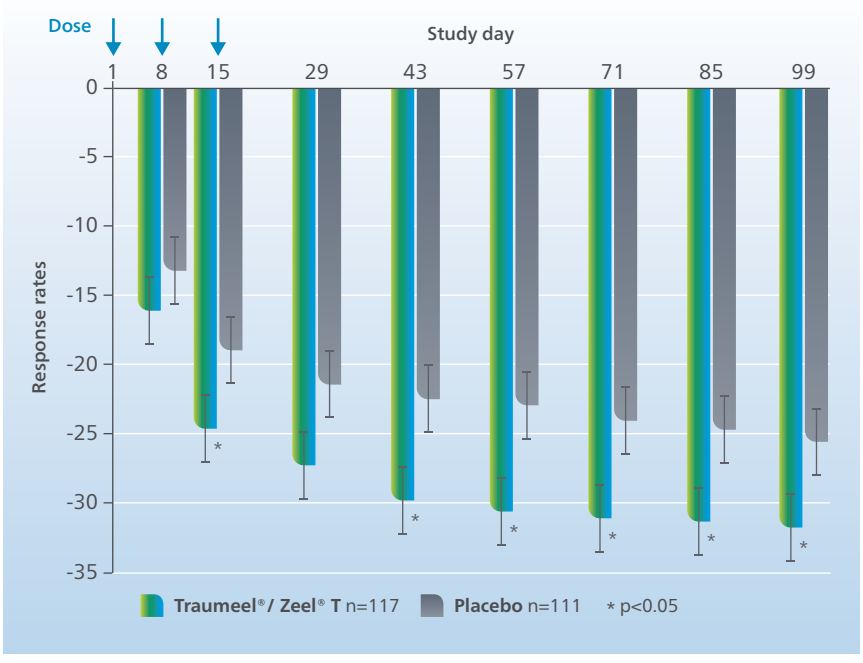


* Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): To assess pain, stiffness, and physical function in patients with hip and / or knee osteoarthritis (OA).

Results

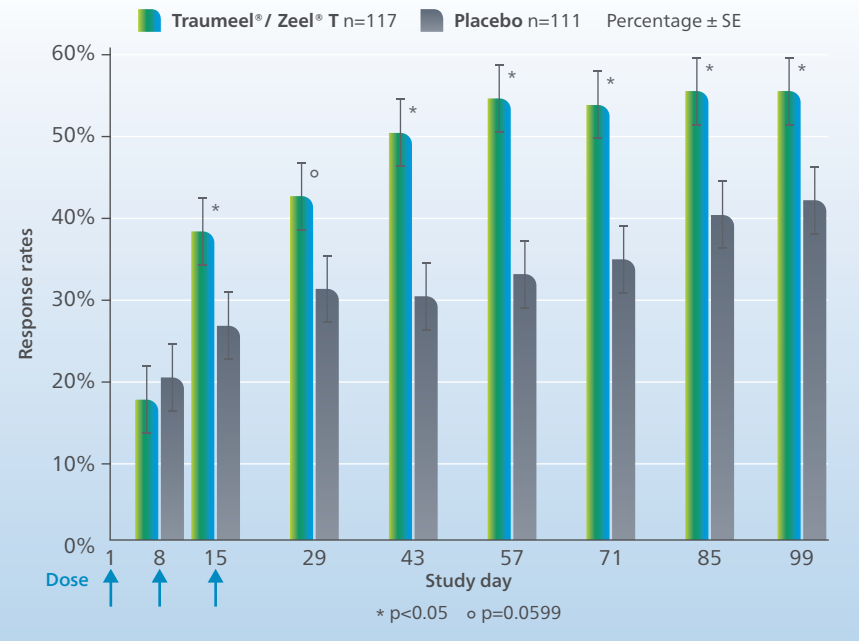
- Treatment arms were well balanced across demographic and baseline characteristics.
- The combination Traumeel®/Zeel® T started to be significantly different ($p<0.05$) for WOMAC A Pain already after the second of 3 injections on Day 15 and was subsequently significantly different on Days 43, 57, 71, 85 and 99 (primary endpoint day) (Figure 13).[59]
- Effect sizes compared with placebo were 0.26, 0.22, 0.30, 0.31, 0.30, 0.25 and 0.25 for Days 15, 29, 43, 57, 71, 85 and 99, respectively, indicating persistent efficacy over time with values comparable or superior to independently reported intra-articular and oral treatment.[30,59]

Figure 13
Mean (± SE) changes from baseline in WOMAC A (Knee Pain Subscale) (Intention-to Treat).[59]



- The proportion of patients achieving a MCID response with Traumeel®/ Zeel® T was significantly greater ($p<0.05$) already after the second of 3 injections on Day 15 and was subsequently significantly different on Days 43, 57, 71, 85 and 99 (primary endpoint day) (Figure 14).[1]
- 50' walk pain was similarly discriminating as was the physician global assessment.
- Total WOMAC and subscores B&C were directionally consistent with WOMAC A.
- There were no related SAEs. AEs were generally mild and unrelated to treatment. Local knee-related AEs, lab assessments, ECGs and vital signs were unremarkable and similar between treatments.
- Periodic Safety Update Reports/Development Safety Update Reports confirmed a favorable safety profile; Traumeel® exposure was at least 117,333,284 ampoules or 2,257,043 Pt-years with cumulative 7 serious and 39 non-serious possibly-related ADRs; Zeel® T was at least 30,168,795 ampoules or 580,169 Pt-years with a cumulative 0 serious and 9 non-serious ADRs.[59]

Figure 14
Percentage of patients achieving decrease in WOMAC Pain subscale score of ≥ 32.6 mm from baseline (Intention-to-Treat).[1]



Conclusion

- The co-administered intra-articular injection of Traumeel® and Zeel® T provided statistically significant and clinically relevant pain relief on days 15 to 99 in comparison to placebo.
- In this double-blind, randomized, controlled trial, a biological/mineral multi-component combination was shown to be a safe and effective treatment for pain in moderate-to-severe knee OA.
- Efficacy effect sizes were consistent with those observed for intra-articular hyaluronic acid, intra-articular corticosteroid and oral NSAIDs.[30,59]
- Unlike oral NSAIDs, the safety profile was benign with no signals of cardiovascular, gastrointestinal or other concerning risks.[59]
- From a qualitative perspective, the risk-benefit relationship for Traumeel® and Zeel® T appears favorable, particularly compared to oral NSAIDs.[30,59]

Non-randomized observational studies

Traumeel® compared with conventional therapy in the treatment of injuries

Reference: Schneider C, Schneider B, Hanisch J, van Haselen R. The role of a homeopathic preparation compared with conventional therapy in the treatment of injuries: an observational cohort study. *Complement Ther Med* 2008,16(1):22–27.

Study design:	Multi-center, prospective, comparative observational cohort study.
Formulation:	Traumeel® in various forms, e.g. tablets, ointment and injections.
Indication(s):	Various musculoskeletal injuries.

Study design

- Patients with various musculoskeletal injuries being treated by German physicians received:
  - Traumeel® as monotherapy or in combination with homeopathic products n=69: 39 male, 30 female; mean age 32.6 years; 67 acute injury, 2 chronic; additional measures taken in 20; co-medication taken by 4.
  - conventional medicines n=64: 31 male, 33 female; mean age 31.6 years; 61 acute, 3 chronic injury; additional measures taken in 26; co-medication taken by 4.
- Additional measures (e.g. functional treatment, compression) and the use of co-medication were permitted and recorded.
- Traumeel® was used in more than one application form by 33% of Traumeel® group.
- Conventional medicines were: analgesics/anti-rheumatics 52%, anticoagulants 16%, anti-inflammatory 7% and miscellaneous 25%; monotherapy in 69% and combination therapy in 31% of patients.

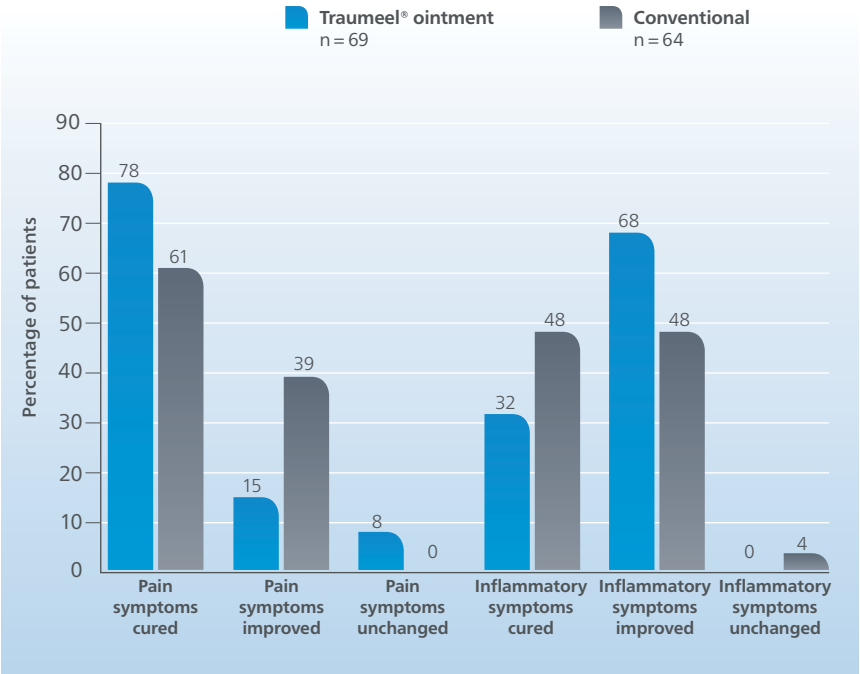
Outcome measures

- Primary: rate of resolution of the principal and secondary symptoms at the end of therapy.
- Secondary: time until symptomatic improvement and treatment outcome as assessed by the physician.

Results

- The principal symptom (most commonly pain, then inflammation) had resolved completely at the end of therapy in 41 patients (59.4%) in the Traumeel® group vs. 37 patients (57.8%) in the conventional group (Figure 15).

Figure 15
Changes in the principal symptoms of pain and inflammation at the end of the treatment period.



- Most patients showed improvement in the principal symptom within 4 days: 49 (71%) in the Traumeel® group and 31 (48%) in the conventional treatment group.
- Cox's proportional hazard regression analysis of the time until improvement shows a greater benefit with Traumeel®: unadjusted hazard ratio 0.95 (95% CI 0.67–1.37), adjusted (for diagnosis, symptoms, age, etc.) hazard ratio 0.94 (95% CI 0.56–1.37). or complications.
- Treatment compliance was judged to be good in both groups, but appeared to better in patients receiving Traumeel®: compliance reported as "very good" in 72% of Traumeel® patients compared with 49% of conventionally treated patients.

Conclusions

- Traumeel® is as effective as conventional medicines in the management of mild to moderate injuries/trauma.
- This study contributes to the evidence for the broad clinical effectiveness of Traumeel® in the treatment of acute injuries and trauma.

Traumeel® compared with diclofenac 1% gel for acute symptomatic treatment of tendinopathy

Reference: Schneider C, Klein P, Stolt P, Oberbaum M. A homeopathic ointment preparation compared with 1% diclofenac gel for acute symptomatic treatment of tendinopathy. *Explore* 2005;1(6):446–452.

Study design: Non-randomized, observational study.
Formulation: Traumeel® ointment
Indication(s): Tendinopathies of varying etiologies.

Study design

- Patients with tendinopathies of varying etiologies were treated with:
  - Traumeel® ointment n=122: 63 male, 59 female; mean age 47.8 years; tendinopathy.
  - Affecting elbow 47, wrist 24, ankle 18, shoulder 16, knee 13.
  - diclofenac 1% gel n=235: 108 male, 127 female; mean age 47.9 years; tendinopathy.
  - Affecting elbow 77, wrist 46, ankle 39, shoulder 36,knee 24.
- Maximum duration of treatment 28 days.
- Traumeel® applied: with bandage 46.7%, twice daily 15.6%, three times daily 57.4%, 4 times daily 26.2%; number of daily applications reduced during course of treatment 19.7%.
- Diclofenac applied: with bandage 28.5%, twice daily 18.3%, three times daily 60.9%, four times daily 18.3%; number of daily applications reduced during course of treatment 10.6%.

Outcome measures

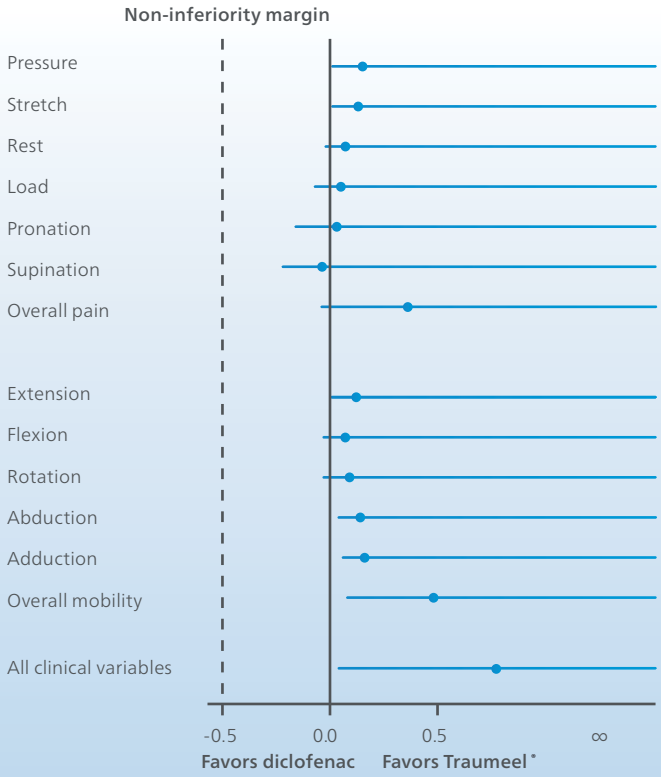
- Efficacy variables: symptomatic changes (pain and mobility), severity of tendinopathy, time to first symptomatic improvement.
- Compliance (very high, high, moderate or low) and tolerability.

Results

- The degrees of improvement in pain and mobility variables were highly similar between treatment groups.
- In most cases, symptoms started to improve after 3–7 days: lack of symptomatic improvement within 28 days was reported in 2.5% of Traumeel® group and 7.7% of diclofenac group.
- In global evaluation of therapies verdicts of “very good” or “good” were given in 88% of Traumeel® cases and 82% of diclofenac cases (p=0.09).

- Non-inferiority analysis showed that Traumeel® was non-inferior to diclofenac for all variables assessed. For most variables, differences trended toward favoring the Traumeel® group (Figure 16). In particular, Traumeel® showed greater benefits on mobility. However, as this study was designed to show non-inferiority and did not include a superiority hypothesis, the possibility of superiority of Traumeel® over diclofenac on mobility variables could not be confirmed using these data.

Figure 16
Point estimate and one-sided 95% confidence interval for the difference between scores for Traumeel® and control for all variables.



(Positive values indicate a favorable effect of Traumeel®; negative values favor the diclofenac group. The border of non-inferiority is shown as a dotted line. The zero line indicates no differences between therapeutic effects.)

- Treatments were well-tolerated ("very good" was reported in 92.5% and 87.9% of Traumeel® and diclofenac patients, respectively), with no treatment-related adverse events. Compliance was "high" or "very high" n both treatment groups in >95% of cases.

Conclusion

Traumeel® ointment is an effective and well-tolerated alternative to diclofenac 1% gel for the acute symptomatic treatment of patients with tendinopathy of varying etiology.

Traumeel® compared with NSAIDs for symptomatic treatment of epicondylitis

Reference: Birnesser H, Oberbaum M, Klein P, Weiser M. The homeopathic preparation Traumeel® S compared with NSAIDs for symptomatic treatment of epicondylitis. *J Musculoskeletal Research* 2004;8(2–3):119–128.

Study design: Non-randomized, observational study.
Formulation: Traumeel® injection.
Indication(s): Epicondylitis.

Study design

- Patients with diagnosed epicondylitis were treated with:
  - Traumeel® injection (local infiltration) n=86: 40 male, 43 female; mean age 48.6 years.
  - NSAIDs (unspecified, mainly diclofenac 51.9%) injection (systemic, mainly intramuscular) n=77: 40 male, 36 female; mean age 45.8 years.
- Other treatments were allowed, e.g. oral analgesics or physiotherapy, but while Traumeel® patients were allowed further injections, they werenot allowed oral NSAIDs: 41.6% of the NSAID group received oral NSAIDs.
- Assessments conducted at weeks 1 and 2.

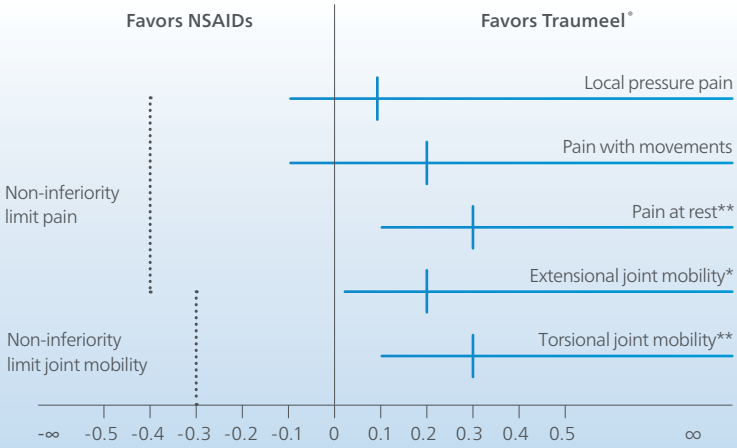
Outcome measures

- Pain: local pressure pain, pain with movement, pain at rest. 5-point scale: 0=no pain, 1=light,2=moderate, 3=strong, 4=severe.
- Mobility: extensional joint mobility, torsional joint mobility. 4-point scale: 1=normal, 2=lightly impaired, 3=moderately impaired, 4=heavily impaired.
- Global assessment of efficacy: time to first improvement, outcome of therapy (very successful, successful, moderate, unsuccessful), compliance (very high, high, moderate, low).

Results

- Both treatments showed similar improvements in all five variables in the first week with no significant differences in time to onset of action.
- Traumeel® showed markedly greater improvements in the variables pain at rest ($p<0.01$), change in extensional joint mobility ($p<0.05$) and change in torsional joint mobility ($p<0.01$) compared with NSAIDs in the second week of treatment (p values from non-inferiority analysis at end of week 2).
- Although the study was designed to assess non-inferiority, the analysis showed Traumeel® to be equivalent to NSAIDs on all variables and trended towards superiority on the variables pain at rest, extensional joint mobility and torsional joint mobility (Figure 17).

Figure 17
Mean difference with 97.5% confidence interval between symptom scores after two weeks for patients treated with NSAIDs (n=77) and Traumeel® (n=86).



* indicates statistically significant superiority of Traumeel® at p<0.05
** indicates significant superiority of Traumeel® at p<0.01

- In global assessment, treatment was judged "very good" or "good" in 71% of Traumeel® patients compared with 44% of NSAID patients (p=0.013).
- Compliance was reported as "very high" or "high" in 92% of Traumeel® patients compared with 81% of NSAID patients (p=0.11).

Conclusion

Traumeel® was at least equivalent to NSAID therapy in reducing pain and improving mobility in the early treatment of epicondylitis.

Traumeel®

Surveillance studies

Drug surveillance for Traumeel® ointment

Reference: Zenner S, Metelmann H. Therapy experience with a homeopathic ointment: results of drug surveillance conducted on 3,422 patients. *Biol Ther* 1994;XII(3):204–211.

Study design:	Multi-centric, post-marketing drug surveillance.
Formulation:	Traumeel® ointment.
Indication(s):	Various traumatic, inflammatory, and degenerative disorders.

Study design

- 378 physicians completed surveys for patients in their care receiving Traumeel® ointment.
  - 3,422 patients: 47.7% male, 51.8% female; mean age 39.9 years.
- The most frequent complaint was sprains, followed in descending order of frequency by degenerative joint disease, hematoma, tenosynovitis, myogelosis, and contusion. Edema, epicondylitis, periarthritis of the shoulder and bursitis were also treated.
- Duration of symptoms was <1 week for 55% of patients, between 1 week and 1 month for 27%, and over 1 month for 18%.
- Traumeel® was the only treatment for 37.7% of patients: 31.3% received non-medical therapy (e.g. application of heat or cold, massage), 9.8% received additional medical therapy (half other preparations of Traumeel®), and 20.3% combined additional medical and non-medical therapy.
- Frequency of application: once daily 14.9%, twice daily 47.5%, three times daily 34.3%, every other day 1.9%.
- Mode of application: alone 48.1%, with dressing 45.0%, with iontophoresis 4.3%.
- Duration of treatment: <1 week 22.4%, 1 week to 1 month 63.6%, 1-3 months 9.8%, 3-6 months 1.6%, >6 months 1.4%.

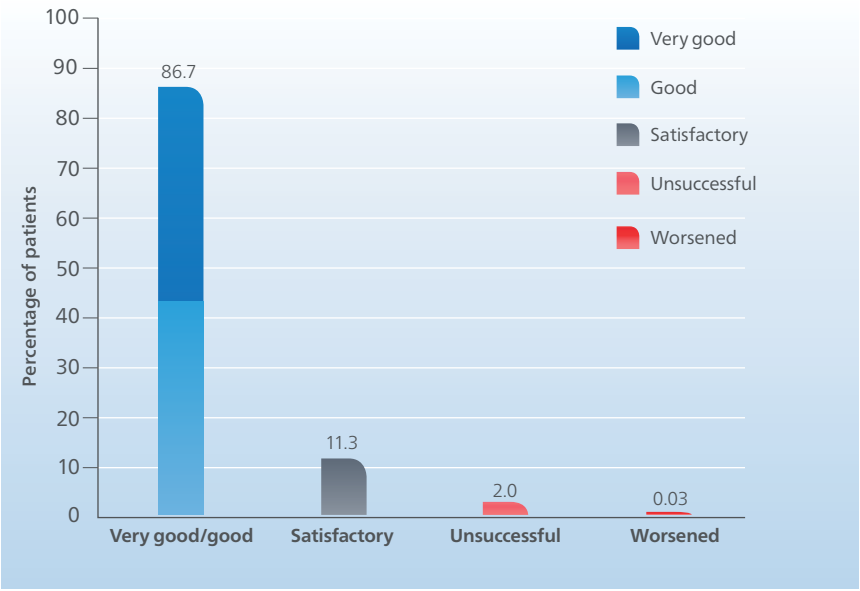
Outcome measures

- Physician-rated therapy outcome: very good, good, satisfactory, unsuccessful, worsened.

Results

- The overall therapeutic results were graded mostly as “very good” (48.3%) or “good” (38.4%). Treatment was “unsuccessful” in only 2% of cases and only one case was reported as “worsening” (Figure 18).

Figure 18
Results of therapy for patients with the biological medication Traumeel® ointment (n=3,422).



- Results were rated as "good" or "very good" in 98.9% of patients with hematoma, 97.0% contusion, 96.3% sprain, 93.2% edema, 92.1% bursitis, 88.1% tenosynovitis, 84.9% myogelosis, 80.4% epicondylitis, 71.6% periarthritis of the shoulder and 54.3% degenerative joint disease.
- Ratings appear higher when Traumeel® was administered without concomitant therapies: 92.2% "good" or "very good" for monotherapy, 86.8% additional non-medical therapy, 86.6% additional medical therapy, and 76.9% additional medical and non-medical therapies.
- Traumeel® was well tolerated (see Clinical safety section, page 56).

Conclusions

Traumeel® satisfies all pre-requisites for low-risk therapy of trauma and its sequelae of soft tissue swelling, as well as inflammatory degenerative processes – and processes associated with inflammation – as manifested in the musculoskeletal system.

Drug surveillance for Traumeel® injection

Reference: Zenner S, Metelmann H. Application possibilities of Traumeel® S injection solution: results of a multicentric drug monitoring trial conducted on 3,241 patients. *Biol Ther* 1992;X(4):301–310.

Study design: Multi-centric, drug monitoring trial.
Formulation: Traumeel® injection.
Indication(s): Various degenerative, traumatic and inflammatory affections.

Study design

- 348 physicians completed surveys for patients in their care receiving Traumeel® injection.
  - 3,241 patients: 49.1% male, 50.5% female; mean age 47.5 years.
- The most frequent complaint was forms of degenerative joint disease (primarily of the knee and hip), followed in descending order of frequency by myogelosis and sprains. Periathropatia humeroscapularis, epicondylitis and tendovaginitis were also treated.
- Duration of symptoms was <1 week for 33.9% of patients, between 1 week and 1 month for 31.0%, and over 1 month for 33.7%.
- Traumeel® was the only treatment for 19.2% of patients: 33.3% received non-medical therapy (e.g. application of heat or cold, massage), 14.9% received additional medical therapy (which could include other preparations of Traumeel®), and 31.1% combined additional medical and non medical therapy.
- Frequency of application: daily 15.2%, 3 times a week 27.7%, twice weekly 40.1%, once weekly 13.6%.
- Manner of application: intramuscular 24.0%, subcutaneous 17.8%, periarticular 14.6%, intra-articular 10.6%, peritendineal 7.0%, intravenous 4.3%, intracutaneous 2.8%, other 18.6%.
- Duration of treatment: <1 week 15.9%, 1 week to 1 month 62.7%, 1-3 months 15.2%, 3-6 months 3.2%, >6 months 2.1%.

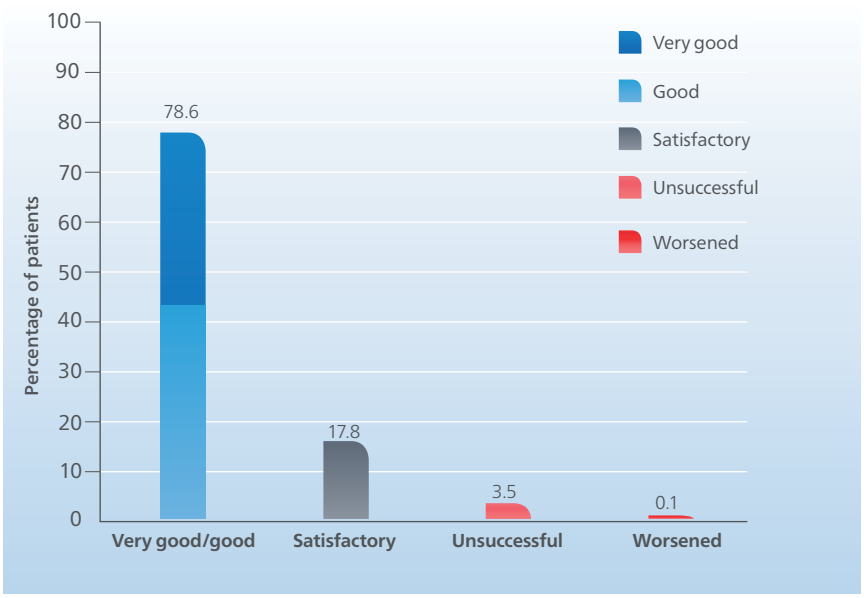
Outcome measures

- Physician-rated therapy outcome: very good, good, satisfactory, unsuccessful, worsened.

Results

- The overall therapeutic results were graded as “very good” or “good” in 78.6% of cases. Treatment was “unsuccessful” in only 3.5% of cases and only five cases (0.1%) were reported as “worsening” (Figure 19).

Figure 19
Results of therapy among patients treated with Traumeel® injection (n=3,421).



- Results were rated as "good" or "very good" in 95.0% of patients with sprains, 86.9% tendovaginitis, 80.1% myogelosis, 78.6% epicondylitis, 74.8% periathropathia humeroscapularis and 59.5% degenerative joint disease.
- Ratings appear higher when Traumeel® was administered without concomitant therapies: 85.2% "good" or "very good" for monotherapy, 79.6% additional non-medical therapy, 82.8% additional medical therapy, and 71.7% additional medical and non-medical therapies.
- The fraction of "good" or "very good" results was greater with shorter administration intervals between injections than for applications with longer time periods between injections; e.g. daily application resulted as "good" and "very good" comments in 90.1%, weekly application only in 68.2%.
- Traumeel® was well tolerated (see Clinical safety section, page 56).

Conclusion

Traumeel® injection solution is effective for therapy of post-traumatic conditions (sprains), as well as inflammatory and degenerative processes affecting the musculoskeletal system.

Drug surveillance for Traumeel® oral treatment

Reference: Zenner S, Weiser M. Oral treatment of traumatic, inflammatory, and degenerative conditions with a homeopathic remedy. *Biol Ther* 1997;XV(1):22–26.

Study design: Multi-center, prospective study.
Formulation: Traumeel® tablets and drops.
Indication(s): Musculoskeletal injuries, inflammatory and degenerative joint conditions.

Study design

- 138 physicians completed surveys for patients in their care receiving Traumeel® tablets or drops.
  - 1,359 patients: 45.3% male, 54.6% female; age <21 12.8%, 21–40 35.2%, 41–60 32.5%, 61–80 16.6% and >80 2.8%.
- The most frequent complaint was bruises, followed in descending order of frequency by sprains, degenerative joint disease, hematomas, carpal tunnel syndrome, frozen shoulder, post-traumatic edema, epicondylitis, and post-operative edema. Joint effusion, dislocations, concussion and bursitis were also treated.
- Duration of symptoms was <1 week for approximately 50% of patients, between 1 week and 1 month for approximately 25%, and over 1 month for about 10%.
- Traumeel® was supplemented with drug or non-drug therapies in approximately two thirds of patients; most frequently with analgesics, anti-inflammatories and medications for circulatory disorders as concomitant drug therapy and application of ice, electrotherapy and physical therapy as concomitant non-drug therapies.
- Mode of application: tablets 69%, drops 29%, both forms 2%.
- Frequency of application: drops – 94% between 5 drops 5 times daily and 30 drops 6 times daily; tablets – 74% 1 tablet 3 times daily.
- Duration of treatment: ≤1 week 23%, 1 – 2 weeks 27%, 2– 3 weeks 22%, 4 – 5 weeks 14%, 6 – 8 weeks 6%, >8 weeks 8%.

Outcome measures

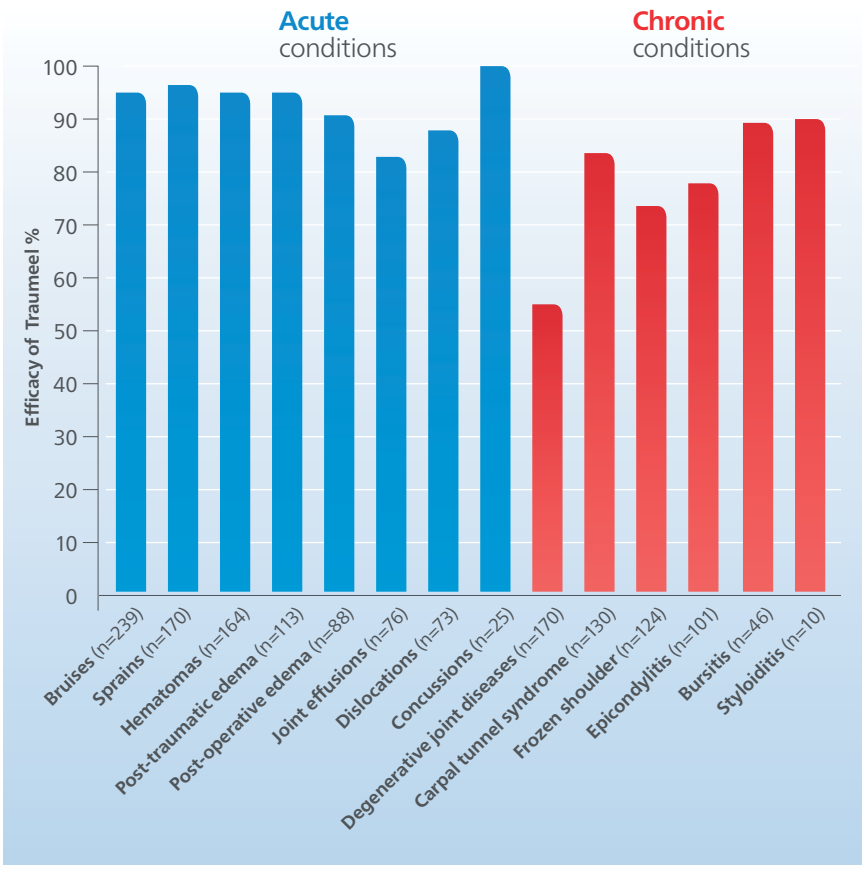
- Time when symptoms began to improve.
- Physician-rated therapy outcome: very good, good, satisfactory, unsuccessful, worsened.

Results

- Improvement in symptoms occurred in the first week for about half of patients, 34% within 1 – 3 weeks and 8% in >4weeks; no improvement noted in 4%.
- In 83% of all cases, therapeutic results were rated as “good” or “very good”. In 13%, treatment was rated as “satisfactory”, while in 4% it was “unsuccessful”.
- There was no difference in the results of treatment with the two different oral forms of the medication.

- Results appeared slightly better in patients receiving Traumeel® alone ("very good" 48.6%) compared with patients receiving concomitant therapy ("very good" 33.7%).
- As may be expected, success rates were high in acute conditions rather than chronic conditions, although even in chronic conditions positive therapeutic results were in achieved in the majority of case (Figure 20).
- Both oral forms of Traumeel® were well tolerated and no adverse reactions were observed.

Figure 20
Good to very good efficacy of Traumeel®, in %*.



Conclusion

Both orally administered forms of Traumeel® are suitable for treating acute post-traumatic conditions, inflammatory and inflammation-related symptoms.

Pediatric studies

Efficacy of Traumeel® in children with musculoskeletal injury

Reference: Ludwig J, Weiser M. Treating pediatric trauma with a homeopathic ointment. *J Biomed Ther* 2001; Summer: 8–11.

Study design: Observational study.
Formulation: Traumeel® ointment.
Indication(s): Acute musculoskeletal injury.

Study design

- Data on children receiving Traumeel® ointment was recorded on standardized questionnaires by 32 pediatricians.
  - n=157: 87 male, 70 female; median age 10, range 0 –12.
- Traumeel® was most frequently prescribed for contusions (31.8%), sprains (23.6%), hematomas (16.6%) and dislocations (7.0%). Other uses of Traumeel® included joint effusions, tenosynovitis, fractures, and epicondylitis.
- The majority of patients (80%) had symptoms for <1 week before treatment.
- Traumeel® was applied 1–3 times daily with or without bandaging in 84% of cases.
- Traumeel® was used as monotherapy in 62%, while 38% received adjuvant therapies, either pharmaceutical (e.g. analgesics or anti-inflammatories) or non-pharmaceutical (e.g. hot/cold packs or massage).
- Duration of treatment: 1 week in two thirds of patients.

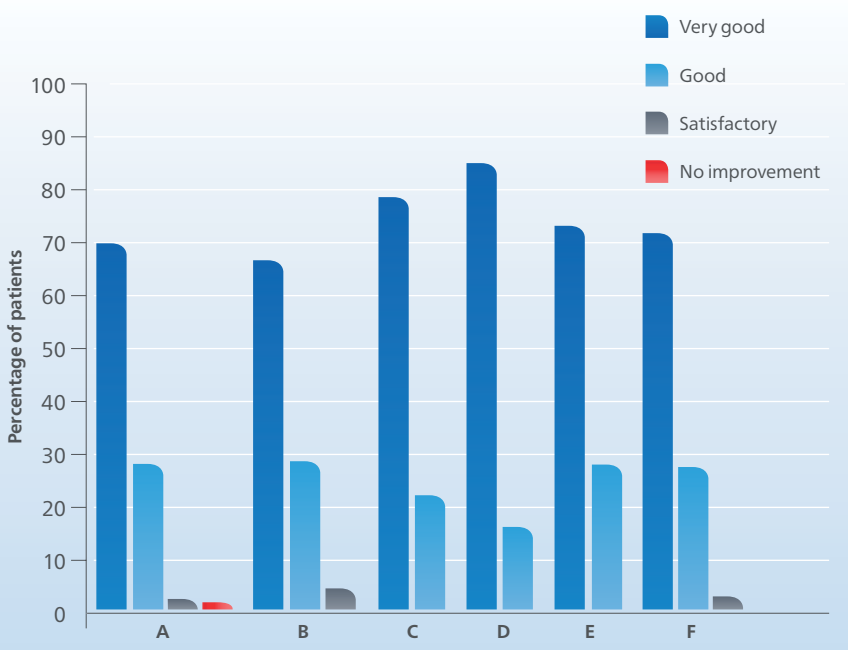
Outcome measures

- Time when symptoms began to improve.
- Physician-rated therapy outcome: very good, good, satisfactory, no improvement, worse.

Results

- Overall analysis of the therapeutic results indicated that the treatment was rated (regardless of age or type of symptoms) as “very good” in 70% of patients and “good” in 27% of patients (Figure 21).

Figure 21
Results of therapy with Traumeel®.



A = total patient population (n=157)
B = contusions (n=50)
C = sprains (n=37)
D = hematomas (n=26)
E = dislocations (n=11)
F = Traumeel® monotherapy (n=97)

- Monotherapy with Traumeel® was rated as "very good" or "good" in 98% of patients.
- Symptoms improved within 1 day of application in 7% of patients, and within 1–3 days in two thirds of the patients. A further 24% saw improvement by the end of the first week of treatment.

Conclusions

- Traumeel® proved effective in all pediatric age groups (infants, pre-schoolers and school-age children) and for all of the usage indications reported.
- Traumeel® is reliably effective in treating both blunt trauma and muscle, joint and soft-tissue disorders of varying etiology in pediatric patients.

6 Clinical safety

KEY FACT

Traumeel® is better tolerated and has less side effects than NSAIDs, particularly in patients that may be at risk of excessive bleeding.

In vitro studies

When the possible effects of Traumeel® on the functions of neutrophil cells were tested *in vitro*, it was observed that Traumeel® did not affect functions of neutrophils such as superoxide anion production and adhesion.[55] The lack of any affect on neutrophil functions indicates that Traumeel® is unlikely to interfere with antimicrobial first defenses. At least one of these neutrophil functions are inhibited by many conventional anti-inflammatory and analgesic compounds.

Furthermore, when investigating the adhesion of human platelets to fibrinogen coated surfaces, Traumeel® did not affect platelet adhesion stimulated by two natural agonists (ADP and thrombin).[55] As inflammatory and homeostatic events are interlinked and platelets are involved in inflammatory reactions, the lack of any impact of Traumeel® on platelet function is of interest. Importantly, the normal homeostatic process is unlikely to be affected by Traumeel®, which suggests it could be used in patients at risk of hemorrhagic events.

Clinical studies in adults

Safety

In a four-week study, 20 healthy volunteers (aged 18–75 years) received two Traumeel® oral tablets sublingually, three times a day.[60] Laboratory tests were performed once a week to assess the effect of Traumeel® on complete blood count, liver profile, serum chemistry, bleeding time, coagulation time and the gastrointestinal system.

The results showed that there was no significant effect from baseline to study completion on any measured laboratory parameter. All subjects' vital signs remained stable throughout the study. No significant changes in hematological parameters, including hematocrit, and platelet and neutrophil counts were observed. Laboratory indicators of kidney and liver function remained unchanged, and no significant differences in prothrombin time or partial thromboplastin time were detected from baseline to post treatment. When stool samples were analyzed for occult blood, as an indicator of gastrointestinal toxicity, all results were negative for all subjects throughout the study.[60]

A total of 11 subjects reported 36 adverse events after taking Traumeel®:[60]

- Headache was the most commonly reported adverse event (n=15)
- Other common events included diarrhea and stomach discomfort/ bloating (n=6), and feelings of nausea (n=2)
- All events were considered to be mild (n=30; 83.3%) or moderate (n=6;16.7%) in severity
- No events required Traumeel® to be stopped; all were transient and resolved despite continuation of the study drug

- No adverse event was considered probably or definitely related to ingestion of the study medication
- No severe toxic events were observed and there was no evidence of gastrointestinal bleeding.

While it should be noted that this was not a placebo-controlled study, it was concluded that Traumeel® is safe and well-tolerated in healthy subjects. The authors suggest that Traumeel® should be considered as a safer alternative to NSAIDs, particularly in patients with conditions, or receiving medications, that affect normal coagulation.[60]

KEY FACT

In a four-week safety study **Traumeel®** demonstrated no significant effect on any of the laboratory parameters measured.

"Traumeel® has anti-inflammatory and analgesic effects and does not inhibit the arachidonic acid pathway of prostaglandin synthesis. Traumeel® deserves consideration as a safer alternative for patients at high risk of gastrointestinal bleeding with conventional NSAIDs."[60]

Randomized-controlled trials

In placebo-controlled trials, no adverse effects were reported with either placebo or Traumeel®.[61,62] In the placebo and active-controlled study, four patients dropped out, these were all in the diclofenac group due to allergic skin reactions.[63] In the active-controlled TAASS study, adverse events were mostly mild or moderate in severity, none was serious and all treatments were equally well tolerated.[2] In MOZArT, the co-administration of intra-articular injections of Traumeel® and Zeel® T demonstrated no related serious adverse events, and adverse events were generally mild and unrelated to treatment. Local knee-related adverse events, lab assessments, ECGs and vital signs were unremarkable and similar between Traumeel®/Zeel® T and placebo.[1]

Tolerability

Post-marketing drug surveillance has shown that tolerability of Traumeel® is good to very good.[64–66]

In 3,467 cases treated with Traumeel® injection there were only 19 reports of undesired effects in conjunction with administration of the medication: 8 cases of local reddening at the site of injection, 1 case of brief local muscle pain, 3 cases of transient irritation of the knee joint, 1 case of pain at the injection site with no further signs of local irritation, 3 cases of a heat sensation at the site of injection, 1 case of circulatory insufficiency, 1 case of general malaise and 1 case of fatigue.[64]

KEY FACT

In observational studies the tolerability of **Traumeel®** was significantly greater than conventional treatment in the management of musculoskeletal injury.

In 3,446 cases treated with Traumeel® ointment there were only 13 reports of undesired effects that were chronologically associated with topical ointment administration.[66] These were local skin irritation and allergic reactions to the medication evidenced by redness of the skin and/or itching. While most reactions were minor and of brief duration, 3 patients experienced more severe reactions and symptoms were relieved on cessation of treatment. Due to the use of other medicinal preparations in these patients, a causal relationship between Traumeel® and these side effects cannot be verified.

Similar to the above drug surveillance studies, surveillance in 1,359 patients treated with oral forms of Traumeel® found that Traumeel® was well tolerated and no adverse reactions were observed.[66]

Observational studies comparing Traumeel® with conventional treatments for musculoskeletal injury show that the tolerability of Traumeel® is significantly greater compared with conventional treatment.[67,68]

In an observational, non-randomized study comparing Traumeel® injection (n=106) with NSAID injection (n=78; mainly diclofenac) in 184 patients with diagnosed epicondylitis over 2 weeks, both treatments were well tolerated.[67] However, a significantly greater proportion of patients receiving Traumeel® reported "very good" tolerability compared with those receiving NSAIDs (88% versus 45%, respectively). Indeed, only three adverse events were reported during the study, all in the NSAID group.

A prospective, observational cohort study compared 69 patients treated with Traumeel® with 64 conventionally treated patients with various musculoskeletal injuries followed over a maximum of 3 months.[68] Tolerability was judged by physicians to be "very good" in a significantly greater proportion of patients receiving Traumeel® compared with conventional treatment (90% versus 50%; p=0.001). Furthermore, there were no adverse events reported in the Traumeel® group, while 6 adverse events were reported with conventional therapy.

Safety in children

Data in children are limited to one study conducted in 157 children aged 0–12 years, median age 10 years.[69] The use of Traumeel® ointment was rated as having "excellent" or "good" tolerability in all patients by reporting pediatricians. No adverse effects were reported from the use of Traumeel® ointment.

Reported adverse effects

Adverse effects with Traumeel® are extremely rare. Traumeel® exhibits no known adverse renal, hepatic, cardiovascular, gastrointestinal or central nervous system effects. Hypersensitivity reactions can occur in individual cases. Patients with hypersensitivity to any of Traumeel®'s ingredients may, in rare instances, experience an allergic reaction after the administration of Traumeel®.

Skin rash and pruritus and, in rare cases, facial swelling, dyspnea, dizziness and a fall in blood pressure have been observed after treatment with products containing Echinacea extracts.

KEY FACT

No interactions with other medications have been observed following use of **Traumeel®**.

Drug interactions

Traumeel® is not known to interact with any other medications or with any laboratory tests. Systemic use of Traumeel®, via either oral or parenteral administration, can be safely augmented by the application of Traumeel® in a topical dosage form.

Contraindications

Hypersensitivity to Traumeel® or any of its ingredients.

Pregnancy and lactation

Animal reproduction studies have not been performed and the effects of Traumeel® on the unborn fetus are unknown. In pregnancy or suspected pregnancy, Traumeel® should only be used if, in the judgment of the treating physician, the potential benefits outweigh the potential risks to the fetus.

It is not known whether any of the ingredients in Traumeel® are excreted in human milk. Consequently, Traumeel® should be administered with caution to nursing mothers under the close supervision of a physician.

Long-term safety

There is no evidence of tachyphylaxis or addiction following the long-term use of Traumeel®.

No studies have been performed to evaluate the carcinogenicity of Traumeel®, however, in worldwide post-marketing surveillance studies, no evidence of carcinogenicity has been found.[71]

7 Use in clinical practice

KEY FACT

Traumeel® can be considered as a first-line treatment for patients with musculoskeletal injuries and inflammation.

Place in therapy

For patients

Traumeel® is a first-line treatment for patients with musculoskeletal injuries and inflammation. While it is suitable for most patients, it may be particularly suitable for patients who are unable or unwilling to tolerate NSAIDs.

Contraindications to diclofenac[71]

- Hypersensitivity to the active substance or any of the excipients
- Patients who have previously shown hypersensitivity reactions (e.g. asthma, angioedema, urticaria or acute rhinitis) to ibuprofen, aspirin or other NSAIDs
- Patients with a history of, or active, gastrointestinal ulcers, bleeding or perforation (two or more distinct episodes of proven ulceration or bleeding)
- Severe hepatic, renal and heart failure
- During the last trimester of pregnancy
- History of gastrointestinal bleeding or perforation, relating to previous NSAID therapy
- Acute porphyria

Patient groups and conditions in which diclofenac should be used with caution[71]

- The elderly
- Gastrointestinal disorders including history of ulceration, or inflammatory bowel disease
- Hepatic impairment*
- Respiratory conditions including asthma, seasonal allergic rhinitis, nasal polyps, chronic obstructive pulmonary diseases or chronic infection of the respiratory tract
- Renal impairment
- Cardiac impairment
- Hypertension
- Defects of hemostasis, bleeding diathesis or hematologic abnormalities
- Increased cardiovascular risk, including established ischemic heart disease, peripheral arterial disease or cerebrovascular disease, also with risk factors including hypertension, hyperlipidemia, diabetes mellitus, smoking
- Systemic lupus erythematosus and mixed connective tissue disorders
- Women attempting to conceive (may impair fertility)

* The Food and Drug Administration (FDA) issued a warning concerning the potential for elevation in liver function tests during treatment with all products (including topical formulations) containing diclofenac sodium. In post-marketing reports, cases of drug-induced hepatotoxicity have been reported in the first month but can occur at any time during treatment with diclofenac.[14]

Drugs diclofenac can interact with:[71]
Lithium, anticoagulants, antidiabetic agents, ciclosporin, tacrolimus, methotrexate, quinolone antimicrobials, other NSAIDs including COX-2 selective inhibitors, corticosteroids, antiplatelet agents, selective serotonin reuptake inhibitors (SSRIs), diuretics, antihypertensives, cardiac glycosides, mifepristone, baclofen, drospirenone, ketorolac, penicillamine, erlotinib, iloprost, pentoxifylline, sibutramine, venlafaxine, phenytoin, ritonavir, zidovudine.

Results of the large scale randomized study, TAASS, confirm that topical Traumeel, in ointment or gel form, is an effective alternative to topical diclofenac 1% gel for reducing pain and improving function for the treatment of acute ankle sprain.[64]

In addition, the recent MOZArT study investigated patients with moderate-to-severe chronic knee osteoarthritis (OA) randomized to 3 weekly intra-articular co-administration of both Traumeel® and Zeel® T (n=119) or saline (n=113). The significant reduction in pain observed with Traumeel®/Zeel® T versus placebo could provide a safer alternative to the use of long-term NSAIDs for the relief of pain in this chronic condition.[1]

In observational cohort studies Traumeel® has shown significantly better tolerance compared with NSAIDs.[67,68] Post-marketing drug surveillance has shown that adverse reactions to Traumeel® are uncommon and largely limited to mild local reactions at the site of administration.[64–66]

KEY FACT

Traumeel® has demonstrated improved tolerability compared with NSAIDs.

Treatment algorithm

In view of the results from TAASS and the established evidence base, a treatment algorithm has been developed to assist clinicians in the appropriate utilization of Traumeel® in clinical practice.[72,2] An expert panel evaluated the place of Traumeel® in therapy based on clinical trial evidence and personal experience of the product. They concluded that Traumeel® could be considered a therapy of choice in the following conditions: acute, acute exacerbation of chronic condition, and chronic. The treatment algorithm provides multiple treatment options for a broad range of musculoskeletal disorders and demonstrates Traumeel® as a part of the general armamentarium to manage these conditions.[72]

For healthcare professionals

You may be most interested in using Traumeel® in your patients if you are a:

- General practitioner/family practitioner
- Orthopedic surgeon (orthopedist)
- Rheumatologist
- Physician with sports medicine training
- Pharmacist
- Physician with patients unable to take NSAIDs.

Alternatively, you may have patients who are interested in using Traumeel®.

Traumeel® formulations and dosing recommendations

Traumeel® is available in a variety of formulations for flexibility of use and to maximize patient convenience and compliance. It can be obtained in:

- Ointment or gel for topical application
- Oral tablets
- Ampoules of solution for injection.

Medication names, indications and formulas may vary from country to country; package inserts provide country-specific information.

Dosage

Tablets: In general, 1 tablet to be dissolved in the mouth 3 times daily.
Injection solution: In acute disorders daily, otherwise 1–3 times weekly, 1–2 ampoules can be injected intramuscularly, subcutaneously, intravenously, intradermally or peri- and intra-articularly.
Ointment: Apply to the affected parts 2–3 times daily, or if necessary more often, possibly also applying an ointment dressing.
Gel: Apply to the affected parts 2–3 times daily, or if necessary more often.

Note: Do not apply the ointment/gel directly into open wounds.

Pharmaceutical particulars

Storage

Products should not be frozen or exposed to excessive heat.
See packaging instructions for specific storage recommendations of each Traumeel® formulation.

Ingredients

Tablets: 1 tablet containing: Arnica montana D2, Calendula officinalis D2, Hamamelis virginiana D2, Achillea millefolium D3 15 mg each; Atropa belladonna D4 75 mg; Aconitum napellus D3, Mercurius solubilis Hahnemanni D8, Hepar sulfuris D8 30 mg each; Matricaria recutita D3, Symphytum officinale D8 24 mg each; Bellis perennis D2, Echinacea D2, Echinacea purpurea D2 6 mg each; Hypericum perforatum D2 3 mg.
Injection solution: 2.2 ml containing: Arnica montana D2, Calendula officinalis D2, Chamomilla recutita D3, Symphytum officinale D6, Achillea millefolium D3, Atropa belladonna D2 2.2 mg each; Aconitum napellus D2 1.32 mg; Bellis perennis D2 1.1 mg; Hypericum perforatum D2 0.66 mg; Echinacea D2, Echinacea purpurea D2 0.55 mg each; Hamamelis virginiana D1 0.22 mg; Mercurius solubilis Hahnemanni D6 1.1 mg, Hepar sulfuris D6 2.2 mg.

Ointment: 100 g containing: Arnica montana D3 1.5 g; Calendula officinalis Ø, Hamamelis virginiana Ø 0.45 g each; Echinacea Ø, Echinacea purpurea Ø, Matricaria recutita Ø 0.15 g each; Symphytum officinale D4, Bellis perennis Ø 0.1 g each; Hypericum perforatum D6, Achillea millefolium Ø 0.09 g each; Aconitum napellus D1, Atropa belladonna D1 0.05 g each; Mercurius solubilis Hahnemanni D6 0.04 g; Hepar sulfuris D6 0.025 g. Excipients: Paraffinum liquidum, cetostearyl alcohol (type A), emulsifying, white soft paraffin, purified water, ethanol, preserved with 13.8 vol.-% ethanol.
Gel: 10 g containing: Arnica montana D3 0.15 g; Calendula officinalis Ø, Hamamelis virginiana Ø 0.045 g each; Echinacea angustifolia Ø, Echinacea purpurea Ø, Chamomilla recutita Ø 0.015 g each; Symphytum officinale D4, Bellis perennis Ø 0.01 g each; Hypericum perforatum D6, Achillea millefolium Ø 0.009 g each; Aconitum napellus D1, Atropa belladonna D1 0.005 g each; Mercurius solubilis Hahnemanni D6 0.004 g; Hepar sulfuris D6 0.0025 g.

Excipients: Carbomers, purified water, sodium hydroxide solution, ethanol. Contains 25 vol.-% alcohol.

Ø = undiluted, i.e. the so-called ‘mother tincture’.

Packaging

Tablets: Packs containing 50 and 250 tablets.
Injection solution: Packs containing 10 and 100 ampoules of 2.2 ml each.
Ointment: Tubes containing 50 and 100 g ointment.
Gel: Tubes containing 50 and 100 g of gel.

8 Summary

- Traumeel® has been used in more than 50 countries around the world for over 60 years, having reached millions of patients with a usage of over 10 million packages a year, of which more than half are ointment and gel.
- Traumeel® is indicated as a first-line treatment for patients with traumatic injuries of all kinds such as sprains, dislocations, contusions, hemarthrosis and effusions into a joint; regulation of inflammatory processes in various organs and tissues, including in particular acute and chronic/degenerative disorders of the musculoskeletal system.
- Traumeel® contains 14 components from natural sources to cover the different aspects of the inflammatory phenomenon.
- Multi-component medications, such as Traumeel®, are aimed at the modulation of inflammatory pathways to restore and maintain homeostasis rather than suppressing them.
- The components of Traumeel® act synergistically to accelerate the healing process.
- Traumeel® has a different mode of action to conventional anti-inflammatory drugs.
- Traumeel® appears to work through complex interactions with the cytokine network, which regulates inflammatory responses.
- Randomized controlled studies have shown that Traumeel® is more effective than placebo and at least as effective as diclofenac, while observational cohort studies have shown Traumeel® to be at least comparable with conventional therapies for the treatment of acute musculoskeletal injury.
- Intra-articular co-administration of Traumeel® and Zeel® T has been shown, in a large randomized controlled trial (MOZArT), to be an effective treatment for pain in OA of the knee and to improve physical function.
- Intra-articular co-administration of Traumeel® and Zeel® T has been shown, in a large randomized controlled trial (MOZArT), to be an effective treatment for pain in OA of the knee.
- The treatment algorithm provides multiple treatment options for a broad range of musculoskeletal disorders and demonstrates Traumeel® as a part of the general armamentarium to manage these conditions.
- Post-marketing surveillance has demonstrated very good tolerability for Traumeel® formulations with very few adverse effects observed.
- Tolerability of Traumeel® has been demonstrated to be significantly greater than with conventional treatments.
- Traumeel® may be particularly suitable for patients who are unable or unwilling to tolerate conventional anti-inflammatory medication, or for those in whom such treatment is contraindicated.

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11 Summary of product characteristics

Traumeel® formulations and dosing recommendations

Traumeel®: Tablets • Injection solution • Ointment • Gel

Compositions: ***Tablets:*** 1 tablet = 301.5 mg containing: Active ingredients: Atropa belladonna D4 75 mg; Aconitum napellus D3, Hepar sulfuris D8, Mercurius solubilis Hahnemanni D8, 30 mg each; Chamomilla recutita D3, Symphytum officinale D8 24 mg each; Achillea millefolium D3, Arnica montana D2, Calendula officinalis D2, Hamamelis virginiana D2, 15 mg each; Bellis perennis D2, Echinacea angustifolia D2, Echinacea purpurea D2 6 mg each; Hypericum perforatum D2 3 mg. Excipients: Lactose monohydrate 6.0 mg; Magnesium stearate 1.5 mg. ***Injection solution:*** 2.2 g containing: Active ingredients: Achillea millefolium D3, Arnica montana D2, Atropa belladonna D2, Calendula officinalis D2, Hepar sulfuris D6, Chamomilla recutita D3, Symphytum officinale D6, 2.2 mg each; Aconitum napellus D2 1.32 mg; Bellis perennis D2 1.1 mg; Mercurius solubilis Hahnemanni D6 1.1 mg; Hypericum perforatum D2 0.66 mg; Echinacea angustifolia D2, Echinacea purpurea D2 0.55 mg each; Hamamelis virginiana D1 0.22 mg. Excipients: Sodium chloride 19.4 mg, water for injections 2179.1 mg. ***Ointment:*** 100 g containing: Active ingredients: Arnica montana D3 1.500 g; Calendula officinalis Ø, Hamamelis virginiana Ø, 0.450 g each; Chamomilla recutita Ø, Echinacea angustifolia Ø, Echinacea purpurea Ø, 0.150 g each; Bellis perennis Ø, Symphytum officinale D4, 0.100 g each; Achillea millefolium Ø, Hypericum perforatum D6 0.090 g each; Aconitum napellus D1, Atropa belladonna D1, 0.050 g each; Mercurius solubilis Hahnemanni D6 0.040 g; Hepar sulfuris D6, 0.025 g. Excipients: Paraffin, liquid 9.342 g; cetostearyl alcohol (type A), emulsifying 8.007 g; white soft paraffin 9.342 g; water, purified 60.579 g; ethanol 96% (V/V) 9.335 g. ***Gel:*** 100 g containing: Active ingredients: Arnica montana D3 1.500 g; Calendula officinalis Ø, Hamamelis virginiana Ø, 0.450 g each; Chamomilla recutita Ø, Echinacea angustifolia Ø, Echinacea purpurea Ø, 0.150 g each; Bellis perennis Ø, Symphytum officinale D4, 0.100 g each; Achillea millefolium Ø, Hypericum perforatum D6, 0.090 g each; Aconitum napellus D1, Atropa belladonna D1, 0.050 g each; Mercurius solubilis Hahnemanni D6 0.040 g; Hepar sulfuris D6 0.025 g. Excipients: Water, purified 74.652 g; ethanol 96% (V/V) 18.653 g; carbomers 1.000 g; sodium hydroxide solution 18% m/m 2.300 g.

Indications: ***Tablets, injection solution, ointment, gel:*** Traumatic injuries of all kinds such as sprains, dislocations, contusions, haemarthrosis and effusions into a joint; regulation of inflammatory processes in various organs and tissues, including in particular acute and chronic/degenerative disorders of the musculoskeletal system.

Contraindications: ***Tablets, injection solution, gel:*** Known allergy (hypersensitivity) to one or more of the ingredients, including plants of the daisy family (Asteraceae) such as Arnica montana (arnica), Calendula officinalis (pot marigold), Matricaria recutita (chamomile), Echinacea (coneflower), Achillea millefolium (yarrow), Bellis perennis (daisy). ***Ointment:*** Known allergy (hypersensitivity) to one or more of the ingredients, including plants of the daisy family (Asteraceae) such as Arnica montana (arnica), Calendula officinalis (pot marigold), Chamomilla recutita (chamomile), Echinacea (coneflower), Achillea millefolium (yarrow), Bellis perennis (daisy) and emulsifying cetylstearyl alcohol.

Special warnings and special precautions for use: ***Tablets:*** Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. ***Injection solution:*** None. ***Ointment:*** Cetylstearyl alcohol may cause local skin reactions (e.g. contact dermatitis). Avoid contact with eyes, mucosae, open wounds or broken skin. ***Gel:*** Avoid contact with eyes, mucosae, open wounds or broken skin.

Side effects: ***Tablets, ointment, gel:*** Allergic (hypersensitivity) skin reactions may occur in very rare cases (i.e. affects less than 1 in 10,000 users). ***Injection solution:*** Allergic (hypersensitivity) reactions (e.g. skin allergies, redness/swelling at the injection site, even up to anaphylaxis) may occur in very rare cases (i.e. affects less than 1 in 10,000 users).

Interactions with other medication: ***Tablets, injection solution, ointment, gel:*** No interactions have been reported, and none are expected due to the homeopathic dilutions.

Pregnancy and lactation: ***Tablets, injection solution, ointment, gel:*** For this product no clinical data on pregnancy and lactation are available. Homeopathic dilutions of the substances present in this medicament are not known to be toxic during pregnancy and lactation. No adverse effects have so far been reported.

Effects on ability to drive and use machines: ***Tablets, injection solution:*** No effects on the ability to drive and use machines have been reported, and none are expected due to the homeopathic dilutions. ***Ointment, gel:*** Not applicable.

Dosage: ***Tablets:*** Standard dosage: Adults (and children 12 yrs. and older): 1 tablet 3× daily; 6–11 yrs. 1 tablet 2× daily; 2–5 yrs.: 1 tablet 1–2× daily; below 2 yrs.: 1 tablet 1× daily. Acute or initial dosage: Adults (and children 12 yrs. and older): 1 tablet every ½ to 1 hr., up to 12× daily, and then continue with standard dosage; 6–11 yrs.: 1 tablet every 1 to 2 hrs., up to 8× daily, and then continue with standard dosage; 2–5 yrs.: 1 tablet every 1 to 2 hrs., up to 6× daily, and then continue with standard dosage; below 2 yrs.: 1 tablet every 1 to 2 hrs., up to 4× daily, and then continue with standard dosage. Method of administration: Preferably allow the tablet to dissolve in the mouth, and then swallow. For children it is possible to crush the tablet and add to a small amount of water. This medicine should be taken away from meals. ***Injection solution:*** Standard dosage: Adults (and children 12 yrs. and older): 1 ampoule 1 to 3× weekly. 6–11 yrs.: ⅔ of an ampoule 1 to 3× weekly; 2–5 yrs.: ½ ampoule 1 to 3× weekly. Acute or initial dosage: Adults (and children 12 yrs. and older): 1 ampoule daily, and then continue with standard dosage; 6–11 yrs.: ⅔ of an ampoule daily, and then continue with standard dosage; 2–5 yrs.: ½ ampoule daily, and then continue with standard dosage. Method of administration: Solution for injection may be administered by the s.c., i.d., i.m., i.a. or i.v. route. ***Ointment, gel:*** Standard dosage: Apply 2× daily, or more often if needed. Method of administration: For external use only. Apply generously to the affected area. Traumeel® may be applied using mild compression bandaging and/or occlusive bandaging.

Overdose: ***Tablets, injection solution:*** No cases of overdose have been reported, and none are expected due to the homeopathic dilutions. ***Ointment, gel:*** No cases of overdose have been reported, and none are expected due to the homeopathic dilutions and external use.

Package sizes: ***Tablets:*** Packs containing 50 and 250 tablets. ***Injection solution:*** Packs containing 10 and 100 ampoules of 2.2 ml each ***Ointment, gel:*** Tubes containing 50 and 100 g.

Zeel® T formulations and dosing recommendations

Zeel® T: Tablets • Injection solution • Ointment

Compositions: ***Tablets:*** 1 tablet = 301.5 mg containing: Active ingredients: Acidum DL-alpha liponicum D6 0.03 mg, Acidum silicicum D6 3.00 mg, Arnica montana D1 0.60 mg, Cartilago suis D4 0.30 mg, Coenzym A D6 0.03 mg, Embryo totalis suis D4 0.30 mg, Funiculus umbilicalis suis D4 0.30 mg, Nadidum D6 0.03 mg, Natrium diethyloxalaceticum D6 0.03 mg, Placenta totalis suis D4 0.30 mg, Rhus toxicodendron D2 0.54 mg, Sanguinaria canadensis D3 0.45 mg, Solanum dulcamara D2 0.15 mg, Sulfur D6 0.54 mg, Symphytum officinale D8 0.15 mg. Excipients: Lactose monohydrate 296.94 mg, magnesium stearate 1.50 mg. ***Injection solution:*** 2.0 g containing: Active ingredients: Acidum DL-alpha liponicum D8 2.0 mg, Arnica montana D4 200.0 mg, Cartilago suis D6 2.0 mg, Coenzym A D8 2.0 mg, Embryo totalis suis D6 2.0 mg, Funiculus umbilicalis suis D6 2.0 mg, Nadidum D8 2.0 mg, Natrium diethyloxalaceticum D8 2.0 mg, Placenta totalis suis D6 2.0 mg, Rhus toxicodendron D2 10.0 mg, Sanguinaria canadensis D4 3.0 mg, Solanum dulcamara D3 10.0 mg, Sulfur D6 3.6 mg, Symphytum officinale D6 10.0 mg. Excipients: Sodium chloride 17.6 mg, water for injections 1747.4 mg. ***Ointment:*** 100 g containing: Active ingredients: Arnica montana D3 1.500 g; Calendula officinalis Ø, Hamamelis virginiana Ø, 0.450 g each; Chamomilla recutita Ø, Acidum DL-alpha liponicum D6 0.010 g, Acidum silicicum D6 1.000 g, Arnica montana D2 0.300 g, Cartilago suis D2 0.001 g, Coenzym A D6 0.010 g, Embryo totalis suis D2 0.001 g, Funiculus umbilicalis suis D2 0.001 g, Nadidum D6 0.010 g, Natrium diethyloxalaceticum D6 0.010 g, Placenta totalis suis D2 0.001 g, Rhus toxicodendron D2 0.270 g, Sanguinaria canadensis D2 0.225 g, Solanum dulcamara D2 0.075 g, Sulfur D6 0.270 g, Symphytum officinale D8 0.750 g. Excipients: Cetostearyl alcohol (type A), emulsifying 8.007 g; ethanol 96% (V/V) 9.565 g; paraffin, liquid 9.342 g; white soft paraffin 9.342 g; water, purified 60.810 g.
Indications: ***Tablets, injection solution, ointment:*** Arthrosis/osteoarthritis, and/or rheumatic joint diseases.
Contraindications: ***Tablets, injection solution, ointment:*** Known allergy (hypersensitivity) to one or more of the ingredients.
Special warnings and special precautions for use: ***Tablets:*** Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. ***Injection solution:*** None. ***Ointment:*** Cetylstearyl alcohol may cause local skin reactions (e.g. contact dermatitis). Avoid contact with eyes, mucosae, open wounds or broken skin.
Side effects: ***Tablets, injection solution:*** Like all medicinal products, homeopathic medicines may cause side effects. In isolated cases transient skin allergies have been reported. The frequency of these effects is not known. ***Ointment:*** Like all medicinal products, homeopathic medicines can cause side effects in isolated cases, such as transient allergic reactions. The frequency of these effects is not known.
Interactions with other medication: ***Tablets, injection solution, ointment:*** No interactions have been reported, and none are expected due to the homeopathic dilutions.
Pregnancy and lactation: ***Tablets, injection solution, ointment:*** For this product no clinical data on pregnancy and lactation are available. Homeopathic dilutions of the substances present in this medicament are not known to be toxic during pregnancy and lactation. No adverse effects have so far been reported.
Effects on ability to drive and use machines: ***Tablets, injection solution:*** No effects on the ability to drive and use machines have been reported, and none are expected due to the homeopathic dilutions. ***Ointment:*** Not applicable.
Dosage: ***Tablets:*** Standard dosage: Adults (and children 12 yrs. and older): 1 tablet 3× daily; 6–11 yrs. 1 tablet 2× daily; 2–5 yrs.: 1 tablet 1–2× daily. Acute or initial dosage: Adults (and children 12 yrs. and older): 1 tablet every ½ to 1 hr., up to 12× daily, and then continue with standard dosage; 6–11 yrs.: 1 tablet every 1 to 2 hrs., up to 8× daily, and then continue with standard dosage. Method of administration: Preferably allow the tablet to dissolve in the mouth, and then swallow. For children it is possible to crush the tablet and add to a small amount of water. This medicine should be taken away from meals. ***Injection solution:*** Standard dosage: Adults (and children 12 yrs. and older): 1 ampoule 1 to 3× weekly. 6–11 yrs.: ⅔ of an ampoule 1 to 3× weekly. Acute or initial dosage: Adults (and children 12 yrs. and older): 1 ampoule daily, and then continue with standard dosage; 6–11 yrs.: ⅔ of an ampoule daily, and then continue with standard dosage. Method of administration: Solution for injection may be administered by the s.c., i.d., i.m., i.a. or i.v. route. ***Ointment:*** Standard dosage: Adults (and children 12 yrs. and older): Apply 2 to 4× daily, 6–11 yrs.: Apply 2 to 4× daily. Method of administration: For external use only. Apply a thin layer over the affected area.
Overdose: ***Tablets, injection solution:*** No cases of overdose have been reported, and none are expected due to the homeopathic dilutions. ***Ointment:*** No cases of overdose have been reported, and none are expected due to the homeopathic dilutions and external use.
Package sizes: ***Tablets:*** Packs containing 50 and 250 tablets. ***Injection solution:*** Packs containing 10, 50 and 100 ampoules of 2.0 ml each. ***Ointment:*** Tubes containing 50 and 100 g.

12 Disclaimer

This brochure contains helpful health information based on scientific data and is intended for educational purposes only. The information and/or treatment recommendations are not meant as a specific treatment for any individual and should not be construed as a substitute for or a contradiction of professional treatment recommendations by an attending physician or other qualified healthcare professional. Heel is not liable for any damage or loss caused or alleged to be caused, directly or indirectly, based on use of the information provided herein. Be aware that medication names, indications, and/or formulas may vary from country to country and package inserts may provide country specific information.

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