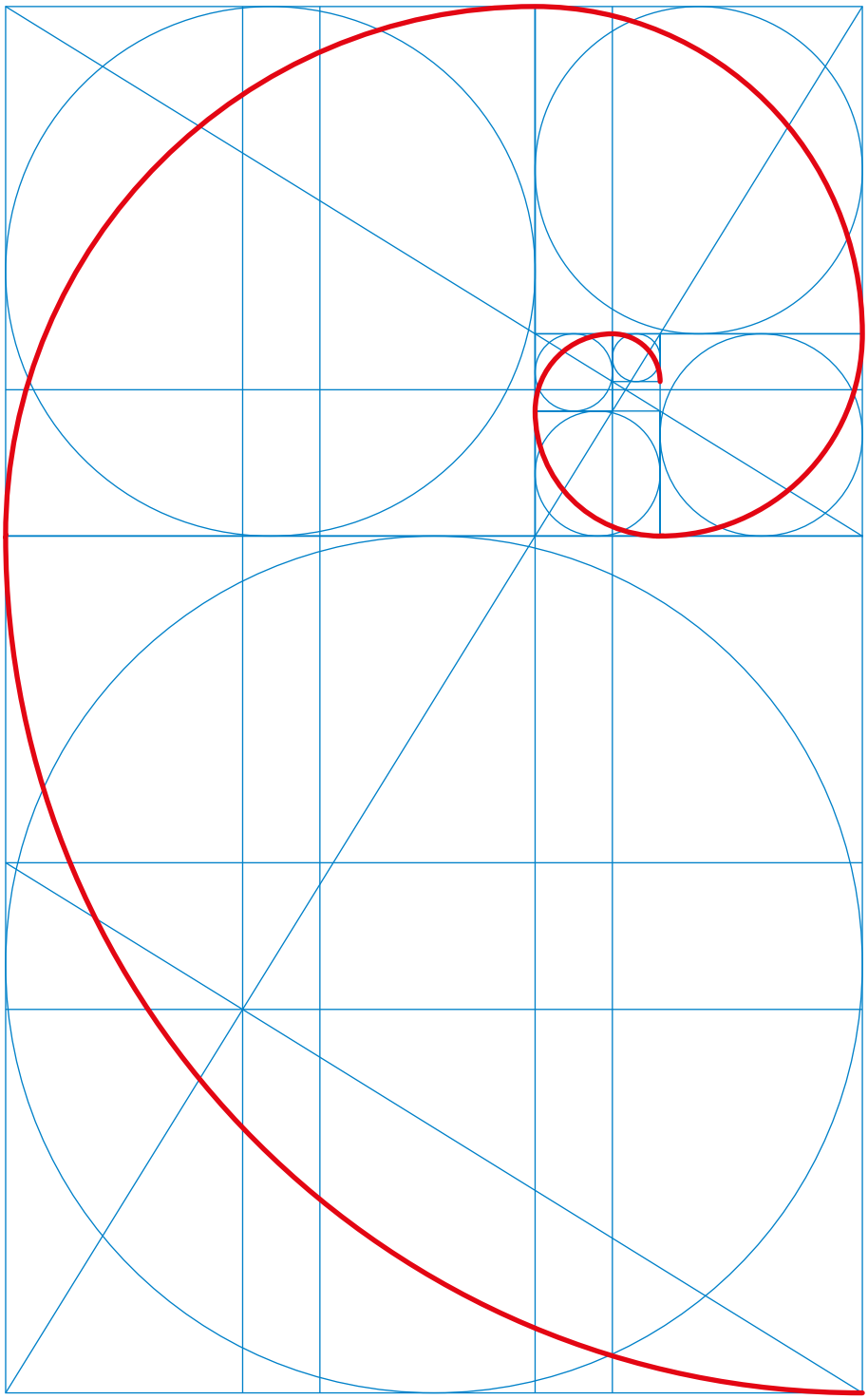
Traumeel®



PRODUCT MONOGRAPH

8th edition, November 2022

023/22

Biologische Heilmittel Heel GmbH
Dr. Reckeweg-Straße 2-4, 76532 Baden-Baden, Germany
Phone +49 7221 501-00

www.traumeel.com
www.inflammres.com
www.heel.com

CONTENTS

1 OVERVIEW

Inflammation is associated with almost every major human disease and is a major player in musculoskeletal disorders (MSD). It is a crucial part of the healing process, and its primary physiological purpose is to restore tissue homeostasis.

If the normal process of **inflammation resolution** fails, it can lead to excessive or chronic inflammation, which is detrimental to recovery, giving rise to a plethora of chronic inflammatory diseases with eventual loss of organ function.

Traumeel® is a multitarget, multicomponent medication that supports inflammation resolution, accelerates the healing process, and provides sustained recovery from injury.

Traumeel® is used in **treatment** of various inflammatory conditions including injuries, especially of the musculoskeletal system, where a proresolution therapy is desirable, or when co-morbidities prohibit the use of a single-target approach. 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. According to the research, Traumeel® regulates the inflammatory process in different organs and tissues, including acute, chronic, and degenerative disorders of the musculoskeletal system.

Traumeel® contains 14 components (plant extracts and minerals) combined to cover the different aspects of the inflammatory process. It has a different mode of action to conventional anti-inflammatory drugs, and a **multitarget effect** on chemical, cellular and tissue mediators which regulate inflammatory responses. The components of Traumeel® act synergistically to accelerate the process, which was shown in state-of-the-art next-generation sequencing technologies, genomics, and pre-clinical studies.

Traumeel® has a **well-established efficacy and safety profile**:

- 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.
- 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. A therapeutic algorithm has been developed to assist clinicians in the appropriate utilization of Traumeel® in clinical practice. Sporting institutions in Italy, Spain and Germany acknowledge Traumeel's efficacy and safety in their respective consensus guidelines or recommendations.
- The MOZArT (Management of Osteoarthritis of the Knee with Zeel And Traumeel Injections) study is a large randomized controlled trial. It demonstrated that Traumeel® and Zeel® co-administered intra-articular injections are significantly superior to placebo in reducing knee pain in subjects with moderate-to-severe pain associated with knee osteoarthritis.

- Tolerability of Traumeel® has been demonstrated to be significantly greater than with conventional treatments.
- Safety studies have indicated that Traumeel® is unlikely to interfere with antimicrobial first defences, 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.
- Traumeel® is suitable for patients requiring first-line treatment for musculoskeletal injuries and inflammation. It may be particularly suitable for patients who are unable to tolerate conventional anti-inflammatory medication, or for those in whom such treatment is contraindicated.
- Investigation of the efficacy and place in therapy of Traumeel® is ongoing, with further randomized controlled trials underway.

Heel is committed to research; an Atlas of Inflammation Resolution (AIR) was jointly created by Heel, Rostock University (Germany) and Harvard Medical School. Researchers are providing the most detailed understanding of acute inflammation and inflammation resolution to date.

Heel supports real-world clinical research; healthcare professionals are encouraged to share their clinical experiences by submitting clincal case reports. Further information is available on www.heel.com

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, in osteoarthritis.[Lozada 2017, González de Vega 2013, Schneider 2011]

MUSCULOSKELETAL INJURIES

Epidemiology of musculoskeletal injury

Worldwide, musculoskeletal conditions are the leading contributor to disability. An estimated 1.71 billion people have musculoskeletal conditions, with low back pain being the single leading cause of disability. These numbers are increasing as the population ages. Chronic conditions limit mobility and can lead to early retirement and reduced well-being.[WHO 2021]

The most prevalent lower limb musculoskeletal injury in physically active populations are lateral ankle sprains (LASs).[Gribble 2016, Waterman 2010] They also have a high prevalence in the general population and pose a substantial healthcare burden. Treatment for acute LAS is quite variable, with many patients returning to activity in a short period of time; however, half of the population may never seek initial care.[Gribble 2016] In a systematic review and meta-analysis of prospective epidemiological studies lateral ankle sprain was also the most commonly incurred type of ankle sprain based on incidence rate units of athlete exposure, years and hours when compared with medial and syndesmotic ankle sprains. The authors reported an estimated incidence rate of 0.93/1000 athlete-exposures (defined as 1 athlete participating in 1 competition or practice).[Doherty 2014]

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.[Bahr 2005] Female athletes are at a 2–9 fold increased risk for ACL injury compared with male athletes competing in the same sport. The highest risk sports are soccer, basketball, lacrosse and volleyball.[Vaudreuil 2020] Most patients with acute ACL tears are younger than 30 at the time of their injury.[Friel 2013] ACL injuries increase osteoarthritis risk resulting in early onset osteoarthritis and were associated with pain, functional limitations, and decreased quality of life.[Lohmander 2007]

Tendon disorders are common and lead to significant disability, pain, healthcare cost and lost productivity. A wide range of injury mechanisms exist leading to tendinopathy or tendon rupture.[Kauz 2011, Thomopoulos 2015] Lateral epicondylitis (tennis elbow), stenosing tenosynovitis (trigger finger), Achilles' tendinopathy, and rotator cuff lesions are some of the most common tendinopathies.[Speed 2001] It is interesting to note that more tennis elbows probably result from industrial work, gardening, or carpentry than from sport. Pain and dysfunction are the main symptoms of tendinopathy, while clinical signs such as swelling or thickening of the tendon are variable.[Kaux 2011]

Classification of musculoskeletal injuries

Periarticular soft tissue complaints include localized disorders of tendons, ligaments, muscles, fascia, and joint capsules.[Speed 2001]

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.[Speed 2001]

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.[Speed 2006]

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.[Heng 2011, Reinke 2012, Demidova-Rice 2012, Sorg 2017] The inflammatory response has defined phases involving different sets of mediators and cell types. First, injury of soft tissue results in a non-specific physiologic response that activates a series of pro-inflammatory events.

Physiologic response to soft tissue injury.[Heng 2011, Reinke 2012, Demidova-Rice 2012, Sorg 2017]

- 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.

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'.

After the initial inflammatory response (usually within 24 hours), the inflammatory process should move to inflammation resolution, with both proinflammatory and proresolution mediators present.[Demidova-Rice 2012] 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.[Demidova-Rice 2012] As new tissue is constructed, the original scar tissue is being dissolved. The scar eventually decreases in size, and tissue remodeling occurs.

Factors affecting response to injury

For successful management of acute soft tissue injury factors promoting efficient optimal recovery should be maximized.[Brumitt 2015] 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. A proresolution environment should be promoted.

Other factors that can affect the healing process are difficult to modify, but should still be included in 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.[Speed 2006] A poor vascular supply may be an important factor in the chronic evolution of soft tissue injuries such as tendon disorders.

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.[Speed 2006]

Genetic factors are implicated in the etiology of many acute musculoskeletal soft tissue injuries.[Collins 2009] Common musculoskeletal soft tissue injuries for which a genetic contribution has been proposed include the Achilles tendon, rotator cuff tendons and cruciate ligaments.

Current treatment options

Successful management of acute musculoskeletal injury requires early recognition, identification of the cause(s), and treatment of any specific pathology.[Speed 2006] 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.[MacAuley 2002, Orchard 2008] 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.[MacAuley 2002] Indeed, it has been observed that even the most accepted treatments find little support when critically evaluated.

Clinical practice guidelines for pain management in acute musculoskeletal injury developed by the Orthopaedic Trauma Association presented evidence-based best practice recommendations and pain medication recommendations. The authors concluded that balancing comfort and patient safety following acute musculoskeletal injury is possible when utilizing a true multimodal approach including cognitive, physical, and pharmaceutical strategies.[Hsu 2019]

RICE

Rest, ice, compression, elevation (RICE) is a mnemonic used to guide the early treatment after acute musculoskeletal injury.[MacAuley 2002] 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.[van den Bekerom 2012]

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) have both anti-inflammatory and analgesic properties. Although therapeutic inhibition of COX-2 by NSAIDs may have beneficial effects in the early phase of inflammation by preventing prostanoid production, it may also be "resolution-toxic," by disrupting the production of anti-inflammatory prostaglandins and lipid mediators, such as LXs (e.g., lipoxin A4 and lipoxin B2).[Sugimoto 2016] 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 and ulceration.[Sullivan 2007] The COX-2 specific agents (celecoxib) and COX-2 selective agents (etodolac, meloxicam) have a decreased risk of clinically significant GI side effects compared with other NSAIDs, but increased costs and potential cardiovascular risks limit their use.

NSAIDs are commonly used in the treatment of acute soft tissue injuries, yet there is a lack of evidence for long-term benefit and concern over side effects.[Jones 2016, Bisciotti 2018, Vuurberg 2018] 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.[Vuurberg 2018] NSAID use can and does alter certain fundamental processes involved in the normal healing of injured tissues.[O'Connor 2008] Importantly, their use could hinder progression to the proresolution phase of inflammation.[Sugimoto 2016, Loynes 2018]

The use of NSAIDs in treating muscle injury is controversial.[Paoloni 2009] Indeed, the use of NSAIDs is actively discouraged in the treatment of muscle tears.[Fernandez-Jaén 2016] Conditions in which NSAID use requires more careful assessment include ligament injury, joint injury, osteoarthritis, haematoma and postoperatively.[Paoloni 2009]

The Food and Drug Administration (FDA) warning on nonsteroidal anti-inflammatory drugs (NSAIDs).

- *Cardiovascular:* "NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk."[FDA 2005]
- *Gastrointestinal:* "NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events."[FDA 2005]
- In July 2015 the FDA further strengthened the cardiovascular warning to indicate that NSAIDs can increase the chance of a heart attack or stroke, either of which can lead to death. Those serious side effects can occur as early as the first few weeks of using an NSAID, and the risk might rise the longer people take NSAIDs.[FDA 2015]
- In October 2020 the FDA issued a warning that use of NSAIDs around 20 weeks or later in pregnancy may cause rare but serious kidney problems in an unborn baby. This can lead to low levels of amniotic fluid surrounding the baby and possible complications.[FDA 2020]

Corticosteroid injections

Corticosteroid injections have been commonly used treatments for chronic tendon lesions.[Speed 2001] However recent analysis of the evidence base found that while corticosteroids show some effectiveness for short-term pain, long-term use in tendinopathies is deemed ineffective and at times contraindicated.[Irby 2020] Common reported side effects include tissue atrophy, facial flushing, postinjection flare, and hypersensitivity reactions.[Speed 2001]

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

Prevention of complications is one of the most important aspects of patient care in pain management. The most common complications associated with joint, tendon, and muscle injections appear to be infections that have been associated with virtually all of these injections.[Cheng 2007]

Traumeel®: promoting inflammation resolution – 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 healing response seems an appropriate strategy for improving outcomes.[Del Valle Soto 2013] Inflammation resolution is not merely a passive cessation of proinflammatory mechanisms. It is a complex, tightly regulated system of processes that is critical for tissue healing and restoration of function.[Sugimoto 2016, Serhan 2014, Feehan 2019, Jones 2016, De Oliveira 2016]

Traumeel® is a combination of 14 natural ingredients designed to have multiple targets. Latest research including single-molecule transcriptome sequencing demonstrates how a multicomponent, multitarget treatment can potentially promote inflammation resolution and tissue healing.[St Laurent 2017, Jordan 2021] Acceleration of muscle regeneration, via enhancing the expression of pro-myogenic genes and proteins, has also been demonstrated when Traumeel® is used in combination with a calf blood compound.[Langendorf 2019, Belikan 2020] Recent clinical evaluations have supported the potential for Traumeel® to promote inflammation resolution and tissue healing in clinical practice.[Das 2019, Helei 2019]

In a wound-healing model, Traumeel® has been shown to produce biologically significant and consistent changes in hundreds of gene expressions involved in wound healing.[St Laurent 2017] Traumeel's effects on gene expression are consistent with its established effects on inflammation and pain.[St Laurent 2017]

In another model of inflammation, Traumeel® shortened the neutrophil resolution interval by 6 hours.[Jordan 2021] This shortening of the neutrophil resolution interval indicates a reduction in time taken to shift from a proinflammatory response to a proresolution response. Coupled with significantly increased macrophage recruitment,[Jordan 2021] and stimulated synthesis of pro-resolving mediators,[Jordan 2021] evidence for Traumeel's potential to promote inflammation resolution is growing (see Section 4 for more details). All of the formulations of Traumeel® contain 14 components. These are listed in Table 1.

Summary

- Inflammation is a natural, protective response to acute injury.
- After the initial inflammatory response (usually within 24 hours), the inflammatory process should move to inflammation resolution.
- Current treatment options, while often widely used, find little support when critically evaluated. Indeed, some are now thought to be detrimental.
- The cardiovascular and gastrointestinal risks associated with non-steroidal anti-inflammatory drugs (NSAIDs) restrict their use in a large number of patients.
- While short-term use of NSAIDs can provide pain relief, their use could impair the healing process.
- Corticosteroid injections are commonly used, however, there is very little evidence that they provide long-term benefit.
- Traumeel® can provide a different approach to management via the promotion of inflammation resolution.

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.[Arden 2006] OA of the knee is responsible for 83% of the overall OA-related disability burden.[Vos 2012] 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. [Braun 2012, Altman 1986, Spector 1993] 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.[Fries 1980, Felson 2009]

Pharmacological treatments for OA include analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular (IA) injections of steroids and IA injections of hyaluronic acid (IA-HA), commonly referred to as viscosupplementation. [Kirchner 2006] Topical preparations, including capsaicin and NSAIDs, can also be used. [Jordan 2003] The supplements chondroitin sulfate and glucosamine are also commonly used by patients despite a lack of evidence for effectiveness.[Wandel 2010]

Although the usual population associated with OA is the elderly, athletes and younger individuals are also susceptible.[Amoako 2014] The etiology may differ, depending on the population; injuries, occupational activities, and obesity appear to be the most common causes of OA in young and athletic populations.[Amoako 2014] Increased pain tolerance in athletes and young individuals can sometimes make diagnosis challenging. However, in these populations, the treatment of OA does not differ from its management in the general population.

Post-traumatic osteoarthritis (PTOA) develops after joint injury. Patients with anterior cruciate ligament (ACL) injury have a high risk of developing PTOA.[Friel 2013, Luc 2014] As a progressive and chronic condition, PTOA should be treated at an early stage to minimize its long-term effects and prevent the development of end-stage OA.[Riordan 2014, Titchenal 2017]

OARSI guidelines published in 2019[Bannaru 2019] stress the importance of managing patients holistically and tailoring treatment individually, particularly with regard to comorbidities. Thus, topical NSAIDs are recommended for those with no comorbidities and those with GI comorbidities, but not for those with cardiovascular comorbidities. Similarly, oral NSAIDs are not recommended for patients with cardiovascular comorbidities, while regimens providing GI protection (COX-2 inhibitors or combined with proton pump inhibitor) should be used in those with no comorbidities, and potentially, with caution, in those with GI comorbidities. For those with cardiovascular comorbidities pharmacologic options are limited to IA injections of corticosteroids and/or hyaluronic acid.

IA corticosteroid is a common treatment for OA of the knee, however, clinical evidence suggests that the benefit is short-lived, usually one to four weeks.[Aroll 2004] Additionally, concern has been expressed that IA corticosteroid may speed the pace of OA and contribute to joint destruction.[Komplel 2019]

Systematic reviews of IA-HA 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,[Rutjes 2012] while a network analysis comparing the relative efficacy 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.[Bannaru 2015]

Role of inflammation

OA is a multifactorial, degenerative joint disorder, with some key pathophysiological aspects playing central roles.[Thysen 2015] The effects of sub-clinical chronic inflammation in OA are now increasingly being recognized.[Bonnet 2005] In the development of OA, pro-inflammatory cytokines have been shown to be associated with cartilage damage.[Haseeb 2013, Malemud 2010, Fernandes 2002] 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.[Pearle 2007] IL-6 may also play a role in angiogenesis, which is another factor contributing to the pathology of OA.[Walsh 2001, Mentlein 2005]

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). 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,[Haeggstrom 2004] and is implicated in the pathogenesis of inflammation.

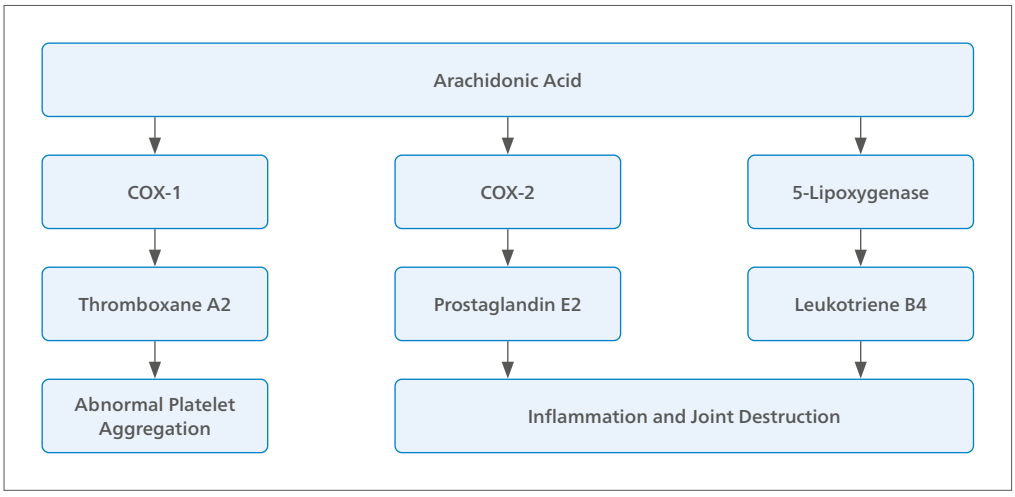


Figure 1 Lipoxygenase (LOX) and cyclooxygenase (COX) enzymes synthesize mediators involved in inflammation and pain

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.[Adatia 2012]

Zeel® T

Zeel® T works by modulating both the 5-lipoxygenase (5-LOX) and COX-1 and -2 pathways. In the recent study by Sanchez et al. Zeel® T reduced several characteristics of OA in a multitarget way by potentially inhibiting cartilage degradation via matrix metallopeptidase 13 (MMP-13) associated pathways and stimulating chondrogenesis via the cellular communication network factor 1 (CCN1) pathway. [Sanchez 2021] 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 acts as a multi-ingredient, multi-target immunomodulation product that principally influences cytokines and TGF-β to attenuate cellular immunity while enhancing bone and cartilage formation.

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).[Bonnet 2005]
- Angiogenesis (formation of new blood vessels).[Bonnet 2005]
- Joint degradation (alteration in cartilage structure).[Bonnet 2005]
- Zeel® T supports cartilage by stimulating extracellular matrix production and may inhibit its degradation. [Sanchez 2021]

The MOZArT study demonstrates that Traumeel® and Zeel® T co-administered intra-articular injections are significantly superior to placebo in reducing knee pain in subjects with moderate-to-severe pain associated with knee osteoarthritis.[Lozada 2017]

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

Summary

- Osteoarthritis (OA) of the knee is a common condition.
- Pharmacological treatments for OA include NSAIDs, intra-articular (IA) injections of steroids and IA-HA.
- To date there are no approved Disease-Modifying Osteoarthritis Drugs (DMOADs) that can slow or alter the progression of OA. [Oo 2021]
- Recent guidelines have suggested that these treatments are individually tailored according to individual patient comorbidities.
- The role of inflammation in OA is now recognised.
- Through their multicomponent and unique formulations, Traumeel® and Zeel® T address multiple targets and pathways to regulate inflammation.
- The MOZArT study demonstrates that Traumeel® and Zeel® T co-administered IA injections are significantly superior to placebo in reducing knee pain in subjects with moderate-to-severe pain associated with knee OA.[Lozada 2017]

3 COMPOSITION

Table 1 Traumeel® product composition

ACHILLEA MILLEFOLIUM (milfoil)	**Ointment** **per 100 g:** D4 0.090 g	**Gel** **per 100 g:** D0 0.090 g	**Tablets** **per tablet:** D3 15.0 mg	**Solution for injection** **per 2.2 ml (= 2.2 g):** D3 2.20 mg	**Drops** **per 100 g:** D3 5.0 g
ACONITUM NAPELLUS (monkshood)	**Ointment** **per 100 g:** D4 0.050 g	**Gel** **per 100 g:** D1 0.050 g	**Tablets** **per tablet:** D3 30.0 mg	**Solution for injection** **per 2.2 ml (= 2.2 g):** D2 1.32 mg	**Drops** **per 100 g:** D3 10.0 g
ARNICA MONTANA (mountain arnica)	**Ointment** **per 100 g:** D4 1.500 g	**Gel** **per 100 g:** D3 1.500 g	**Tablets** **per tablet:** D2 15.0 mg	**Solution for injection** **per 2.2 ml (= 2.2 g):** D2 2.20 mg	**Drops** **per 100 g:** D2 5.0 g
ATROPA BELLADONNA (deadly nightshade)	**Ointment** **per 100 g:** D4 0.050 g	**Gel** **per 100 g:** D1 0.050 g	**Tablets** **per tablet:** D4 75.0 mg	**Solution for injection** **per 2.2 ml (= 2.2 g):** D2 2.20 mg	**Drops** **per 100 g:** D4 25.0 g
BELLIS PERENNIS (daisy)	**Ointment** **per 100 g:** D4 0.100 g	**Gel** **per 100 g:** D0 0.100 g	**Tablets** **per tablet:** D2 6.0 mg	**Solution for injection** **per 2.2 ml (= 2.2 g):** D2 1.10 mg	**Drops** **per 100 g:** D2 2.0 g
CALENDULA OFFICINALIS (calendula)	**Ointment** **per 100 g:** D4 0.450 g	**Gel** **per 100 g:** D0 0.450 g	**Tablets** **per tablet:** D2 15.0 mg	**Solution for injection** **per 2.2 ml (= 2.2 g):** D2 2.20 mg	**Drops** **per 100 g:** D2 5.0 g
MATRICARIA RECUTITA (chamomile)	**Ointment** **per 100 g:** D4 0.150 g	**Gel** **per 100 g:** D0 0.150 g	**Tablets** **per tablet:** D3 24.0 mg	**Solution for injection** **per 2.2 ml (= 2.2 g):** D3 2.20 mg	**Drops** **per 100 g:** D3 8.0 g
ECHINACEA (cone flower)	**Ointment** **per 100 g:** D4 0.150 g	**Gel** **per 100 g:** D0 0.150 g	**Tablets** **per tablet:** D2 6.0 mg	**Solution for injection** **per 2.2 ml (= 2.2 g):** D2 0.55 mg	**Drops** **per 100 g:** D2 2.0 g

ECHINACEA PURPUREA (purple cone flower)	**Ointment** **per 100 g:** D4 0.150 g	**Gel** **per 100 g:** D0 0.150 g	**Tablets** **per tablet:** D2 6.0 mg	**Solution for injection** **per 2.2 ml (= 2.2 g):** D2 0.55 mg	**Drops** **per 100 g:** D2 2.0 g
HAMAMELIS VIRGINIANA (witch hazel)	**Ointment** **per 100 g:** D4 0.450 g	**Gel** **per 100 g:** D0 0.450 g	**Tablets** **per tablet:** D2 15.0 mg	**Solution for injection** **per 2.2 ml (= 2.2 g):** D1 0.22 mg	**Drops** **per 100 g:** D2 5.0 g
CALCIUM SULFIDE (hepar sulfuris)	**Ointment** **per 100 g:** D6 0.025 g	**Gel** **per 100 g:** D6 0.025	**Tablets** **per tablet:** D8 30.0 mg	**Solution for injection** **per 2.2 ml (= 2.2 g):** D6 2.20 mg	**Drops** **per 100 g:** D8 10.0 g
HYPERICUM PERFORATUM (St. John's wort)	**Ointment** **per 100 g:** D6 0.090 g	**Gel** **per 100 g:** D6 0.090 g	**Tablets** **per tablet:** D2 3.0 mg	**Solution for injection** **per 2.2 ml (= 2.2 g):** D2 0.66 mg	**Drops** **per 100 g:** D2 1.0 g
MERCURO-AMIDONITRATE (mercurius solubilis hahnemanni)	**Ointment** **per 100 g:** D6 0.040 g	**Gel** **per 100 g:** D6 0.040 g	**Tablets** **per tablet:** D8 30.0 mg	**Solution for injection** **per 2.2 ml (= 2.2 g):** D6 1.10 mg	**Drops** **per 100 g:** D8 10.0 g
SYMPHYTUM OFFICINALE (comfrey)	**Ointment** **per 100 g:** D4 0.100 g	**Gel** **per 100 g:** D4 0.100	**Tablets** **per tablet:** D8 24.0 mg	**Solution for injection** **per 2.2 ml (= 2.2 g):** D6 2.20 mg	**Drops** **per 100 g:** D8 8.0 g

Excipients

- Ointment – Paraffin, liquid 9.342 g; Cetostearyl alcohol (type A), emulsifying 8.007 g; Paraffin, white soft 9.342 g; Water, purified 60.579 g; Ethanol (96%) 9.335 g; Preserved with 12.7 vol.-% alcohol.
- Gel – Water, purified 74.652 g; Ethanol (96%) 18.653 g; Carbomers (Carbopol 980NF) 1.000 g; Sodium hydroxide solution 18% (m/m) 2.300 g; Contains 24.4 vol.-% alcohol. Purified water, ethanol 96% (V/V), carbomers, sodium hydroxide solution 18% m/m.
- Tablets – Lactose monohydrate 6.0 mg; Magnesium stearate 1.5 mg. Contains lactose! Please see package insert!
- Solution for injection – Sodium chloride 19.4 mg; Water for injections 2179.1 mg.
- Drops – Water, purified 2.0 g; Contains 35 vol.-% alcohol.

Be aware that medication names, indications, and/or formulations may vary from country to country and package inserts may provide country specific information. Therefore, please ensure that the content of any material used is in line with your local laws and any other regulatory and/or medical requirements before implementation. 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.

INFLAMMATION RESOLUTION: A NEW THERAPEUTIC TARGET

Inflammation is a reaction of the host to infectious or sterile tissue damage and has the primary physiological purpose of restoring tissue homeostasis.[Medzhitov 2010, Nathan 2010] Uncontrolled or non-resolving inflammation can both lead to tissue damage, giving rise to a plethora of chronic inflammatory diseases, including metabolic syndrome and autoimmunity pathologies with eventual loss of organ function. Resolution protects the tissue and leads to homeostasis.

Latest research including single-molecule transcriptome sequencing demonstrates how a multicomponent, multitarget treatment can potentially promote inflammation resolution and tissue healing.[St Laurent 2021, St Laurent 2017] Recent clinical evaluations have supported the potential for Traumeel® to promote inflammation resolution and tissue healing in clinical practice.[Das 2019, Helei 2019]

Inflammation resolution is a critical process

The inflammatory response has defined phases involving different sets of mediators and cell types. In the initiation phase proinflammatory mediators initiate the inflammatory cascade in response to injury or infection. Next, inflammation transitions towards resolution and proinflammatory as well as proresolution mediators are present. Resolution is ongoing when other sets of mediators dictate events that terminate the inflammatory process and fully engage in resolution. [Serhan 2005, Sugimoto 2016, Sugimoto 2019]

Inflammation resolution is not merely a passive cessation of proinflammatory mechanisms. It is a complex, tightly regulated system of processes that is critical for tissue healing and restoration of function. Important elements include:[Sugimoto 2016, Serhan 2014, Feehan 2019, Jones 2016, De Oliveira 2016]

- **Neutrophil influx:** swarming of neutrophils from the blood stream into the injury site
- **Lipid mediator class switch:** release of proresolving mediators, such as lipoxins, resolvins, protectins and maresins

- **Efferocytosis:** removal of exhausted, mainly apoptotic neutrophils to prevent tissue damage; many are removed by macrophages
- **Macrophage phenotype switch:** "reprogramming" triggered by efferocytosis, from a proinflammatory to a proresolution phenotype, contributing towards postresolution immune tolerance and prevention of autoimmunity
- **Neutrophil phenotype switch:** "reprogramming" to an anti-inflammatory type, promoting neutrophil reverse migration

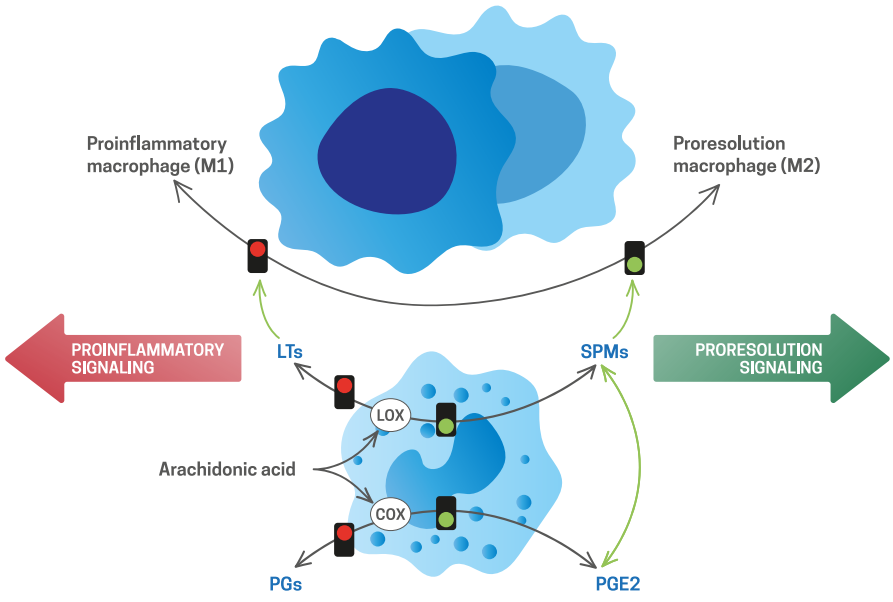
Treatments that suppress inflammation may also suppress its resolution

In severe conditions, an anti-inflammatory strategy is mandatory to prevent tissue destruction or an overwhelming inflammatory process. Alternatively, a proresolution strategy could be considered the treatment of choice.[Fullerton 2016]

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibiting the cyclooxygenase-2 (COX-2) pathway are a mainstay of inflammation treatment. COX-2 promotes biosynthesis of many proinflammatory mediators, but some are equally important for initiation of inflammation resolution (Figure 2). [Sugimoto 2016]

For example, prostaglandin E2 (PGE_2), one of the major products of COX-2, which is usually inhibited by NSAIDs, is involved in:

- A lipid mediator class switch[Sugimoto 2016]
- A macrophage phenotype switch[Sugimoto 2016]
- A neutrophil phenotype switch[Loynes 2018]

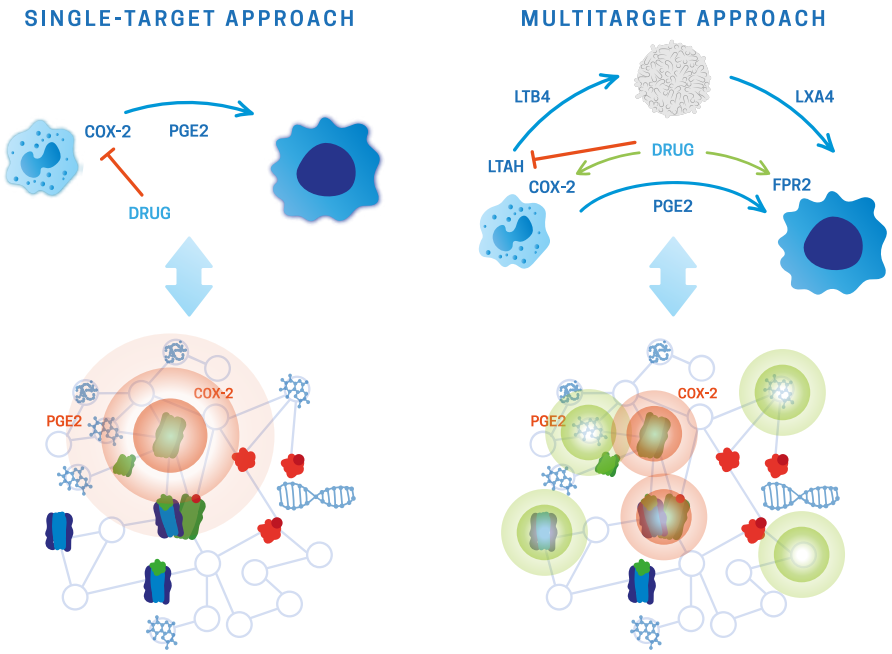


COX, cyclooxygenase; LOX, lipoxygenase; LTs, leukotrienes; PGs, prostaglandins; PGE2, prostaglandin E2; SPMs, specialized proresolving mediators.

Figure 2 Transition to resolution is linked to a switch in cellular phenotypes and chemical mediators.

NSAID treatment may have beneficial effects in the early phase of inflammation by preventing prostanoid production, but may also be "resolution-toxic," by disrupting the production of anti-inflammatory prostaglandins and lipoxins.[Sugimoto 2016]

- Single-target drugs are designed to target a single biological entity (usually a protein) with high selectivity, not taking interactions with other targets into consideration (Figure 3)
- Due to network complexity of disease biology, single-target drugs may have unwanted "ripple" effects on other "off-target" entities
- These "ripple" effects can potentially cause side effects, limiting the effective dose and effectiveness of the single-target drug
- Multitarget drugs can target a larger part of the signaling network (Figure 3)
- They can balance signaling inhibition with promotion by targeting selected synergistic pathways
- The synergistic effect of multiple targets across the signaling network allows the reduction of pharmacological doses and possible side effects

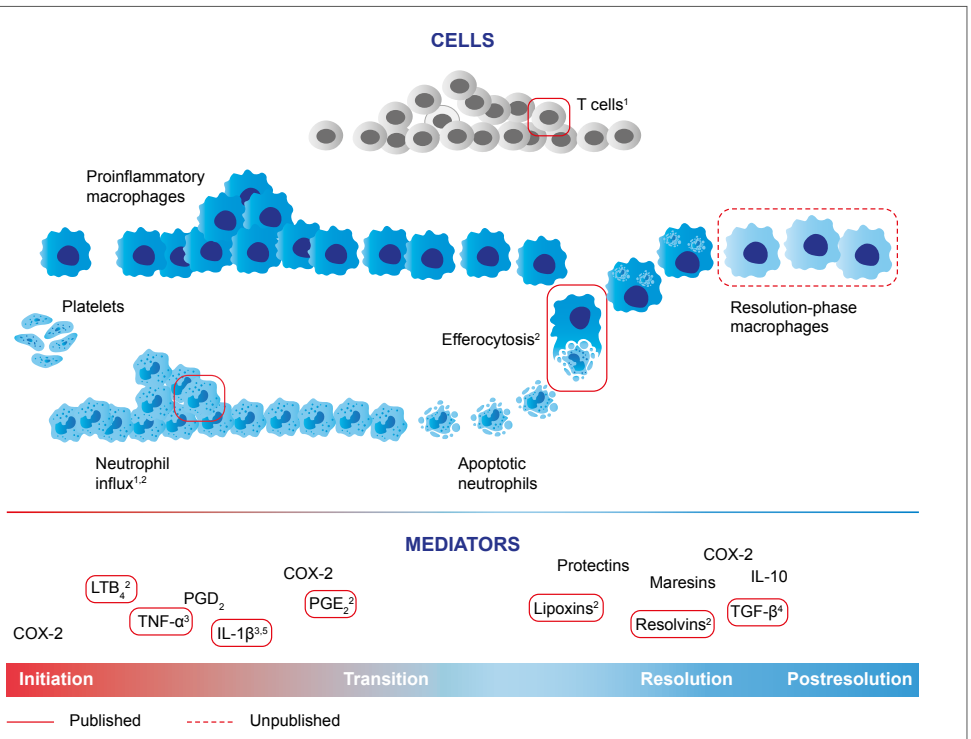


COX-2, cyclooxygenase 2; FPR2, formyl peptide receptor 2; LTB4, leukotriene B4; LTAH, leukotriene A4 hydrolase; LXA4, lipoxin A4; PGE2, prostaglandin E2.

Figure 3 Multitarget drugs provide a better solution for complex processes like inflammation resolution.

Traumeel® is a combination of natural ingredients in low concentration, designed to have multiple targets. Therefore, its mode of action is much broader compared to synthetic drugs. With modern technologies, such as single-molecule transcriptome sequencing and bioinformatics, investigating the action on thousands of signaling events simultaneously is possible.

Traumeel® has demonstrated effects on the mediators and cells involved in inflammation resolution (Figure 4).



COX-2, cyclooxygenase 2; IL-1β, interleukin 1β; IL-10, interleukin 10; LTB4, leukotriene B4; MMP13, matrix metalloproteinase 13; NF-κB, nuclear factor κB; PGD2, prostaglandin D2; TNF-α, tumor necrosis factor α; TGF-β, transforming growth factor β.

1. St Laurent G, et al. *BMC Genomics.* 2021;22(1):854. 2. Jordan PM, et al. *Pharmaceuticals (Basel).* 2021;14(11):1123. 3. Porozov S, et al. *Clin Dev Immunol.* 2004;11(2):143–149. 4. Heine H, Schmolz M. *Biomed Ther.* 1998;16(3):224–226. 5. St Laurent G 3rd, et al. *Front Mol Biosci.* 2017;4:57.

Figure 4 Traumeel® effects on the mediators and cells involved in inflammation resolution.

In vitro studies

Actions of Traumeel®

- Inhibition of the proinflammatory mediators TNF-a, IL-1β and IL-8 in resting as well as activated immune cells preserves defensive functions of granulocytes, lymphocytes, platelets, and endothelial cells.[Conforti 1997, Porozov 2004]
- Stimulation of the anti-inflammatory cytokine TGF-β.[Heine 1998]
- 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.

[Heine 2002, Heine 1998, Conforti 1997, Porozov 2004]

Pre-clinical studies

Actions of Traumeel®

- Broad range of anti-inflammatory and immunomodulatory effects in vitro and in vivo.[St Laurent 2017, St Laurent 2021, Jordan 2021]
- Wound healing and antioxidative effects were also demonstrated in animal models.[St Laurent 2017]
- Significant edema volume reduction of up to 15% seen with Traumeel® in carrageenan-induced edema test.[Conforti 1997]
- A significant reduction in acute local inflammation (first phase of adjuvant arthritis) in adjuvant arthritis model in rats.[Conforti 1997]
- At 3 and 5 hours post intra-paw injection of a small amount of homologous blood, local inflammation was significantly lower in rats treated with Traumeel® compared with controls.[Lussignoli 1999]
- Levels of IL-6, a pro-inflammatory cytokine, were significantly reduced by 45% in Traumeel®-treated rats compared with controls at 5 hours post blood injection.[Lussignoli 1999]
- Traumeel® may reduce muscle damage and inflammatory response following an acute bout of eccentric exercise. [Muders 2016]
- Traumeel induces differentiation of primary human skeletal muscle cells. [Langendorf 2019]
- Traumeel® accelerates inflammation resolution demonstrated by faster reduction of inflammatory cells, polymorphonuclear leukocytes (PMNs) in an animal model.[Jordan 2021]

In silico research/bioinformatics

New technologies allow us to study networks of inflammation resolution. In silico is the term scientists use to describe the modeling, simulation and visualization of biological and medical processes in computers. In silico models can integrate various types of data, including DNA, RNA, protein, metabolic products and more. In silico models link processes to clinical outcomes or other endpoints, such as biomarkers and predictive markers. They have an important role in toxicology studies, as well as other areas.

Wound-healing model: transcriptomics

While DNA remains static, RNA is constantly changing. The transcriptome is the set of all RNA molecules, including mRNA, rRNA, tRNA, and other noncoding RNAs produced in the cell. Unlike the genome, RNA is able to vary under the influence of external environmental conditions.[Kahl 2015, Manzoni 2018, Berg 2020] Studying transcriptome changes is an ideal tool to analyze drug effects.[Manzoni 2018, Debnath 2010]

In the St Laurent et al. study Traumeel® produced biologically significant and consistent changes in hundreds of gene ontologies involved in wound healing.[St Laurent 2017]

Traumeel® regulates a number of gene ontologies in the interleukin family. One example amongst others is IL1-β. Traumeel® delays and attenuates the strong increase in IL1-β mRNA expression in the 12–24 hour period after wounding.[St Laurent 2017] (Figure 5). This is consistent with Traumeel's known action to reduce the pain of inflammation in other indications.[Schneider 2011, González de Vega 2013]

Transcriptomic studies have demonstrated that Traumeel® treatment modulates several major wound repair pathways.[St Laurent 2017, St Laurent 2021]

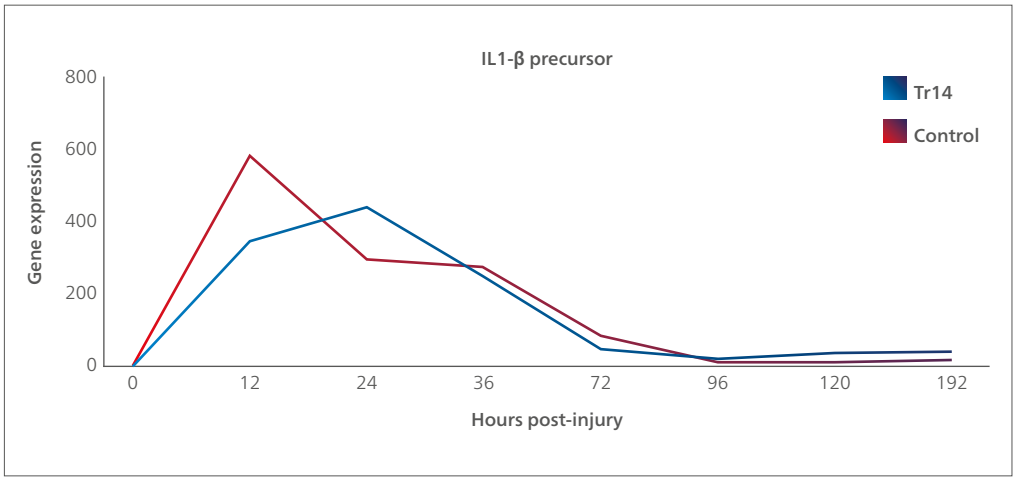


Figure 5 The effect of Tr14 on select transcripts in the interleukin pathway[St Laurent 2017]

- Early effects involved the wound repair and response to stress pathways.[St Laurent 2017]
- Later effects tended to involve the wound contraction and anti-apoptotic pathways necessary for efficient wound closure.[St Laurent 2017]
- Diclofenac, via effects upon the prostaglandin pathway, affected hundreds of transcripts, but in different cellular pathways.[St Laurent 2021]
- In key pathways, such as the defense response and cell motility, diclofenac's effects were often opposite to that of Traumeel®.[St Laurent 2021]
- Although Traumeel® and diclofenac share many inflammation-related pathways, diclofenac is more active at earlier proinflammatory stages, while Traumeel® is more active at a later wound healing stage.[St Laurent 2021]

Overall, genome-wide transcriptional analyses suggest that Traumeel® modulates different inflammatory processes than diclofenac with little overlap. It seems to be due to its multicomponent, multitargeted nature.[St Laurent 2017, St Laurent 2021]

Wound healing model

Actions of Traumeel®

- Traumeel® produced biologically significant and consistent changes in hundreds of gene ontologies involved in wound healing.[St Laurent 2017]
- Hundreds of differentially regulated gene ontologies compared to the saline control.[St Laurent 2017]

- Traumeel® ointment and injection have common and specific effects on gene expression, offering additional rationale for the different administration routes.[St Laurent 2017]
- Traumeel's effects on gene expression are consistent with its established effects on inflammation and pain.[St Laurent 2017]

Zymosan-induced peritonitis model

The zymosan-induced peritonitis model is a self-limited resolving model of acute inflammation with a defined time frame. It enables the quantification of the recruitment and reduction of monocytes and neutrophils into the peritoneal cavity. The time taken to achieve a reduction of 50% in neutrophils is indicative of the speed at which resolution occurs. The model mimics events happening in vivo, however the duration of individual steps needs to be considered with care when knowledge is transferred to humans and outside of a self-limited model.[Cash 2009, Serhan 2018]

Findings

In the recently published in vivo study by Jordan et al. the zymosan-induced murine peritonitis model was used to assess the capacity of Traumeel® to promote inflammation resolution. The results show that Traumeel® supported the recruitment of innate leukocytes and the efferocytotic capacity of macrophages, and positively influenced the inflammation resolution index. The authors suggest that based on these properties, Traumeel® may possess therapeutic potential as an enhancer for the resolution of inflammatory processes.[Jordan 2021]

- Traumeel® shortened the the resolution interval (Ri – interval between T_{max} and T_{50}) with the high dose by 1.3 hours and with the low dose by 5.9 hours.
  - The clearance of neutrophils out of the inflamed area is a major milestone in the resolution of inflammation.
  - The resolution interval is thus indicative of the rate of neutrophil clearance which has drastically been improved by Traumeel®.

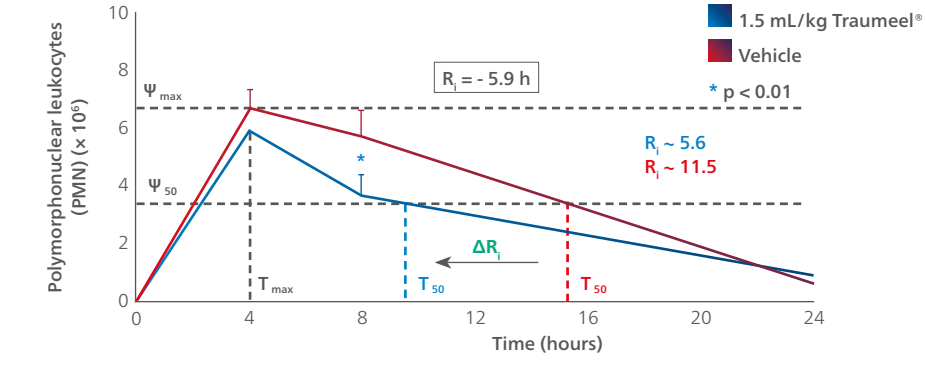


Figure 6 Effects of Traumeel® pre-administered i.p. over 6 days prior murine peritonitis induction, on resolution of inflammation[Jordan 2021]

- Traumeel® may stimulate a switch from pro-inflammatory mediators towards pro-resolving mediators both in vitro (human macrophages) and in vivo (murine model).[Jordan 2021]
- Traumeel® significantly increased macrophage recruitment.
  - Macrophages are needed to remove debris and neutrophils from the inflamed site.
  - Increase in the number of macrophages is believed to have a positive impact on resolution.
  - Is in alignment with shortened neutrophil resolution interval.
- Traumeel® stimulated the synthesis of proresolving mediators: LXA_4, RvD2, RvD5, MaR1 and PD1.
  - Proresolving mediators are the mediators produced as part of the lipid mediator class switch, a hallmark of the resolution phase. Their proresolving function is exerted via several mechanisms and includes effects on:
    - Neutrophils: reduction of PMN (polymorphonuclear leukocyte) infiltration, increased PMN apoptosis.
    - Macrophages: improved efferocytosis and phagocytosis, non-phlogistic monocyte recruitment and reprogramming towards anti-inflammatory and proresolving phenotypes.

Zymosan-induced peritonitis model

Actions of Traumeel®[Jordan 2021]

- Traumeel® promotes resolution of inflammation by increasing specialized pro-resolving mediators (SPM) levels and by enhancing macrophage efferocytosis as well as by shortening the resolution interval in an animal model.
  - Shortened the neutrophil resolution interval by 5.9 hours.
  - Significantly increased macrophage recruitment.

ATLAS OF INFLAMMATION RESOLUTION (AIR)

Recently, an Atlas of Inflammation Resolution (AIR) was created by Heel, together with Rostock University and Harvard Medical School researchers, providing the most detailed understanding of acute inflammation and inflammation resolution to date. The AIR is a comprehensive web-based resource describing all molecules involved in inflammation and its resolution, their interactions, and, most importantly, underlying cardinal processes. It is connected to many public scientific databases such as UniProt, GenBank, and Pubmed, and serves as a portal to these databases. This allows identifying any element on the map, its literature source, and using these databases for drug target identification. [https://www.sbi.uni-rostock.de/research/projects/detail/62]. The AIR is published in Molecular Aspects of Medicine 2020[Serhan 2020]

How is the AIR organized?

The AIR is organized into three layers of structure and function (Figure 7). The top layer is the Phenotype layer, the middle layer is the Process layer, and the bottom layer is the Molecular Interaction Map (MIM). Changes on one layer have an effect and can be visualized on all other layers.

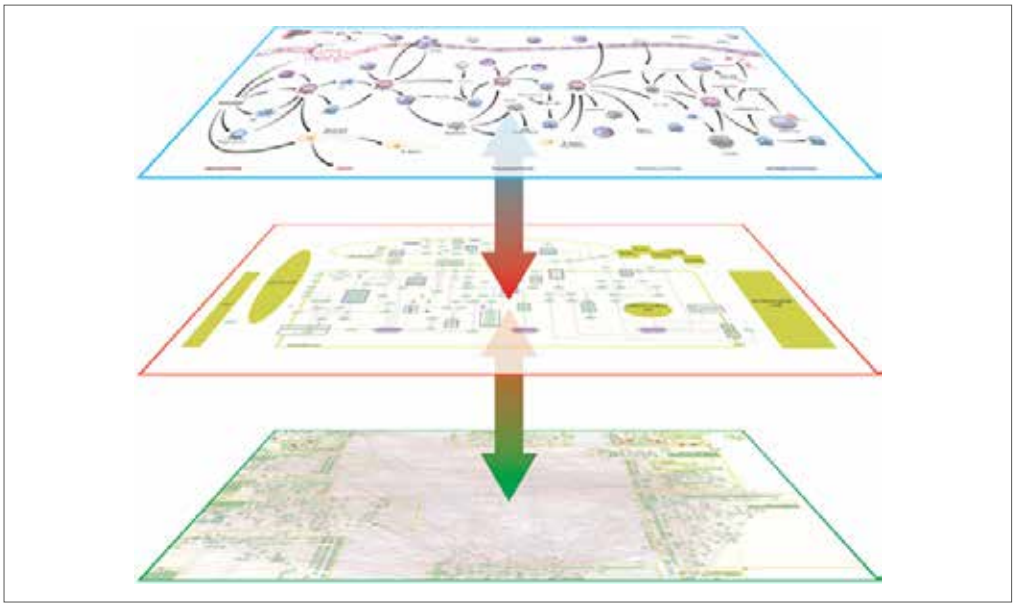


Figure 7 Atlas of Inflammation Resolution[Serhan 2020]

The Phenotype layer (top) shows cells and mediators. Clinicians are generally interested in connecting their patients to this layer. The Process layer (middle) describes key molecules / pathways regulating the top layer and is suitable for research scientists, looking to generate new hypothesis on the mechanistic insights of disease phenotype regulation. The MIM layer (bottom) depicts all molecular details and interactions in acute inflammation and IR. This layer is suitable for data integration and analysis, i.e. experimental data can be mapped onto this layer and then analyzed and visualized.

Clinical support for proresolution and tissue healing effects of Traumeel®

Recent clinical evaluations of postoperative recovery suggest that use of Traumeel® can promote enhanced tissue recovery and facilitate faster return of function.[Das 2019, Helei 2019]

Post-periodontal surgery[Das 2019]

- Prospective, randomized, triple-blind split-mouth clinical trial in 20 patients.
- Patients receiving Traumeel® experienced significantly less pain than those receiving ibuprofen.
- Consumption of Traumeel® was also lower compared with ibuprofen.
- Compared with patients receiving ibuprofen, Traumeel® resulted in significantly less edema and improved tissue colour, indicating improved tissue healing.

- No adverse events were observed with Traumeel® while three patients reported adverse events when receiving ibuprofen.

Alveolitis post-dental extraction [Helei 2019]

- Comparison of complex drug therapy (Traumeel® initially plus antimicrobial at purulent stage; main observation group, 38 patients) with conventional treatment (20 patients).
- By the second day, the use of Traumeel® had an anti-inflammatory and analgesic effect, which made it possible to improve the general condition of the patient, and reduce the manifestations of local inflammatory process and pain.
- Postoperative wound healing processes progressed rapidly and efficiently in the main observation group. Cytological studies showed:[Helei 2019]
  - A progressive decrease in neutrophil granulocytes count over 5 days of observation from 87.8 to 57.0%; appearance of colonies of fibroblasts from 0 to 22.0% and active epitheliocytes (6.1%) at the end of observation in the main group.
    - In patients of the control group (conventional treatment) the processes of regeneration were less intense and tended to chronization of inflammation – the number of neutrophilic granulocytes decreased from 83.2 to 68.2% in 5 days, the number of fibroblasts increased from 0 to 9.4%; the number of active epitheliocytes was 1.7%.
    - The number of lymphocytes increased significantly (up to 12.3%) with conventional treatment, which was not observed in the main group and which can be considered as a sign of chronization of inflammation.
  - Jaw function recovery averaged 3.4 ± 0.1 days longer in the conventional treatment group.
  - Normalization of the overall condition of the body and its temperature response was delayed by an average of 4.8 ± 0.2 days compared to the main observation group.

Summary

- Recent advances in the field of inflammation resolution have shown that resolution is an active process dictated by proresolving mediators.
- The active nature makes it an ideal pharmacological target and proresolution strategies are novel concepts in the treatment of injury and inflammatory disease.
- Some proinflammatory mediators also play an important role in resolution. Thus the use of anti-inflammatory treatments should be weighed carefully and used in a more targeted way.
- An anti-inflammatory and/or proresolution approach should be chosen depending on the needs of the patient.
- Traumeel® has been shown to possess proresolution activity in preclinical experiments by modulating multiple targets.
- These effects support our hypothesis that Traumeel® promotes resolution which is consistent with its established clinical effects on inflammation and pain.
- Recent clinical evaluations support a proresolution effect of Traumeel® in clinical practice.

5 TRAUMEEL® STUDIES – INDICATIONS

A range of studies evaluating Traumeel® in different indications have demonstrated its effectiveness compared with placebo, NSAIDs and conventional therapy.

INDICATION	THERAPIES	STUDY
Randomized, double-blind trials		
Ankle sprains	Traumeel® ointment vs placebo ointment	Zell 1989
Acute ankle sprain	Traumeel® ointment, Traumeel® gel vs 1% diclofenac gel	González de Vega 2013
Acute musculoskeletal injuries	Traumeel® ointment vs placebo ointment	Böhmer 1992
Osteoarthritis of the knee	Traumeel® in co-administration with Zeel® T (intra-articular injections)	Lozada 2017
Observational studies		
Epicondylitis	Traumeel® injections vs unspecified NSAID (mainly diclofenac)	Birnesser 2004
Tendinopathy of varying etiology (based on excessive tendon load rather than inflammation)	Traumeel® ointment vs diclofenac 1% gel	Schneider 2005
Various musculoskeletal injuries	Traumeel® (tablets and gel) vs conventional management	Schneider 2008

INDICATION	THERAPIES	STUDY
Pediatric study		
Acute musculoskeletal injury (observational study)	Traumeel® ointment	Ludwig 2001
Surveillance studies		
Variety of injuries (e.g. sprains, posttraumatic edema), and degenerative and inflammatory conditions (arthrosis and epicondylitis)	Traumeel® tablet or drop forms (69% tablets, 29% drops, 2% both). One-third of patients were treated without other therapies (drug and non-drug)	Zenner 1997
Variety of injuries, and degenerative and inflammatory conditions	Traumeel® ointment. Used exclusively by 38% of patients; adjuvant medications taken by 30% of patients; 52% received nonmedication therapies	Zenner 1994
Variety of injuries, and degenerative and inflammatory conditions	Traumeel® injection. Used exclusively by 17% of patients; adjuvant medications taken by 47% of patients; 65% received nonmedication therapies	Zenner 1992

RANDOMIZED CONTROLLED CLINICAL TRIALS

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

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	FORMULATION	INDICATION(S)
Randomized, controlled, blinded study.	Traumeel® ointment and gel.	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 8).
- 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 55.7 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).

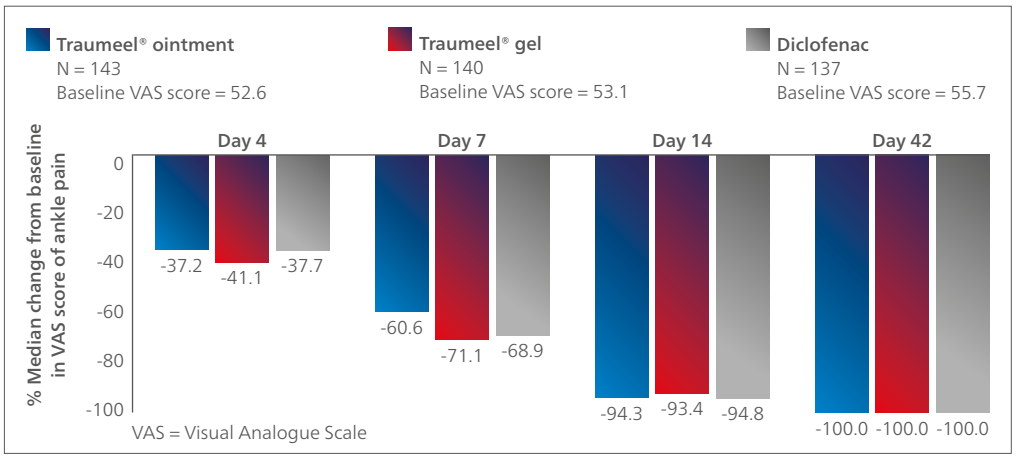


Figure 8 Median percentage change in VAS pain scores from baseline.

- 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 9).
- 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.

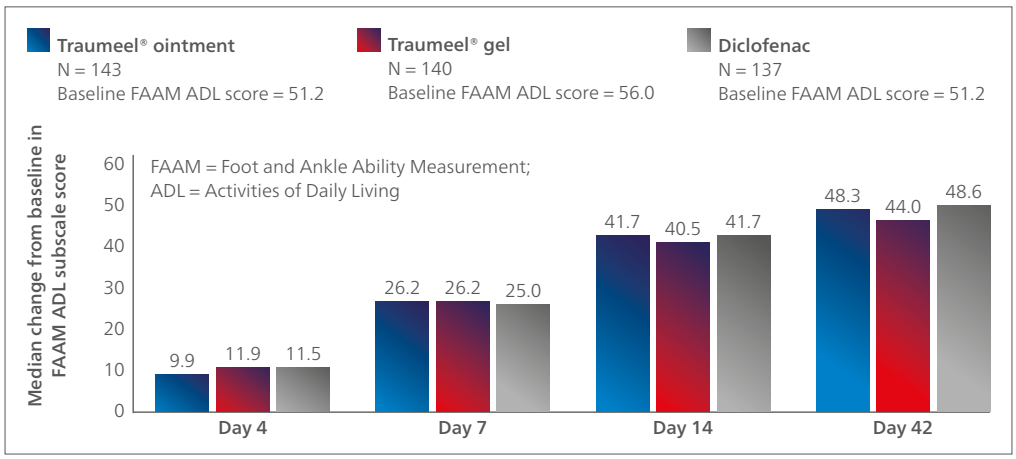


Figure 9 Median change from baseline in FAAM ADL subscale score.

- An overview of the primary endpoint results, day 7, is shown in Figure 10.
- Confidence intervals were above the predefined lower equivalence margin (0.40), demonstrating that Traumeel® ointment and gel are non-inferior to diclofenac gel 1%.

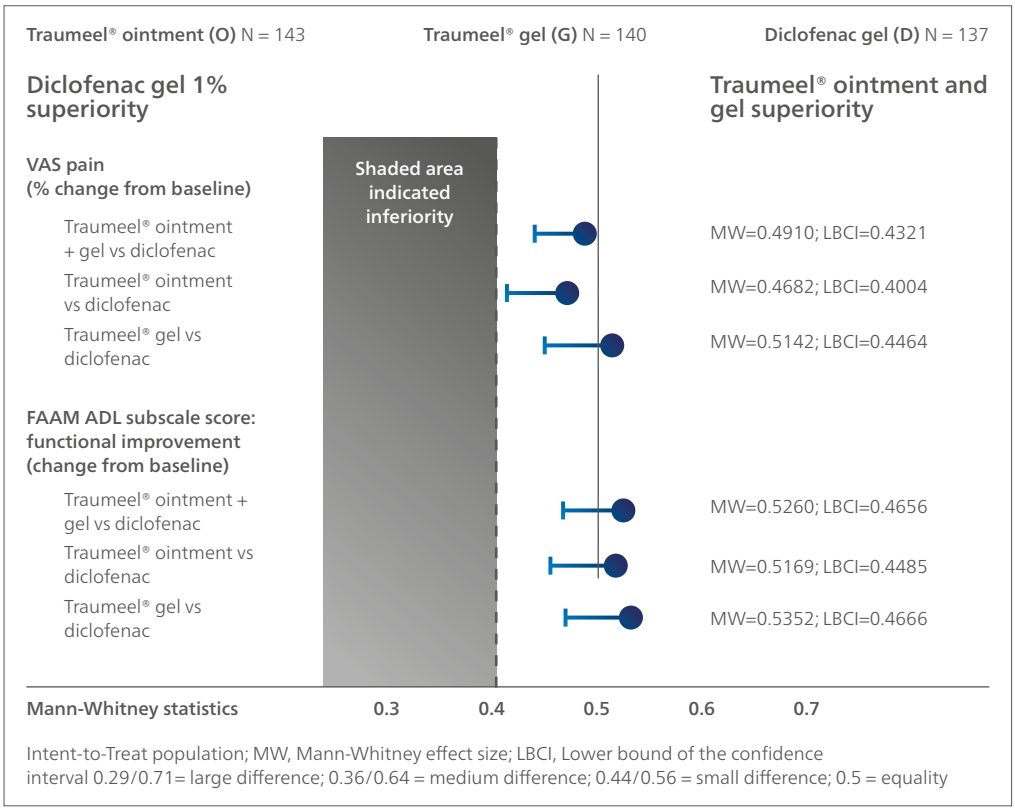


Figure 10 Traumeel® (ointment and gel) is non-inferior to diclofenac gel 1% in reducing pain and improving function (day 7).

- 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.

	Traumeel® ointment N = 143	Traumeel® gel N = 140	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)

Table 3 Secondary efficacy variables

- 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

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	FORMULATION	INDICATION(S)
Randomized, placebo-controlled double-blind study.	Traumeel® ointment.	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

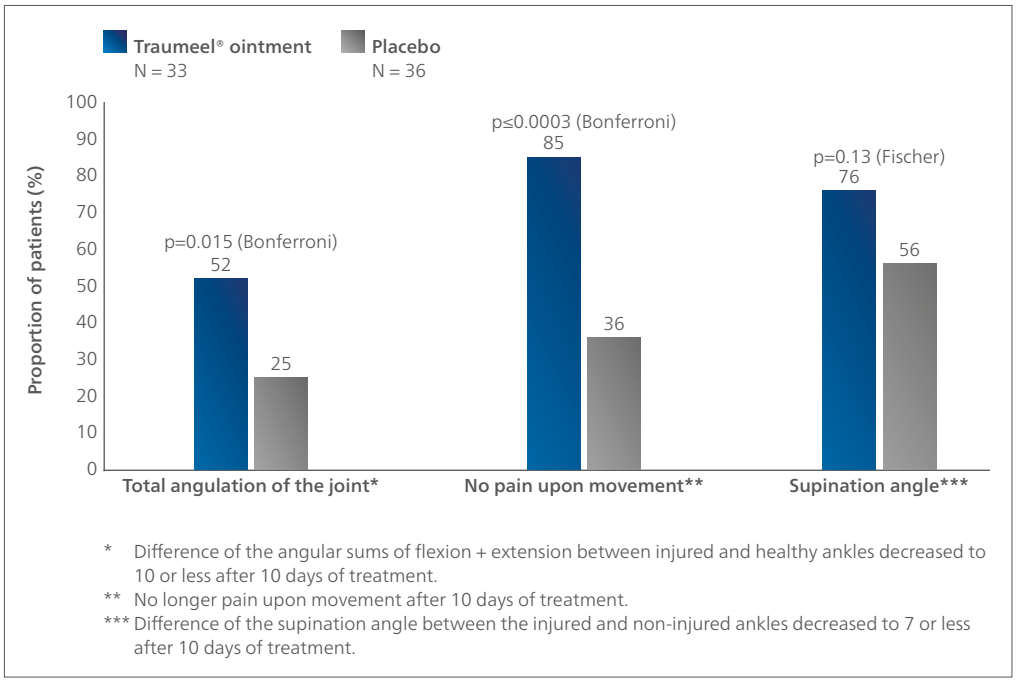
- Primary end point: a pilot study identified the difference in total angulation of the joint – measured in extension and flexion between affected and non-affected joints – as a quantifiable objective measure for the degree of improvement in ankle mobility.
- Secondary end points:
  - the inversion angle (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 11).
- 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 11 and 12).
- 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 12).



* 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 11 Proportion of patients achieving "success" in the different end points.

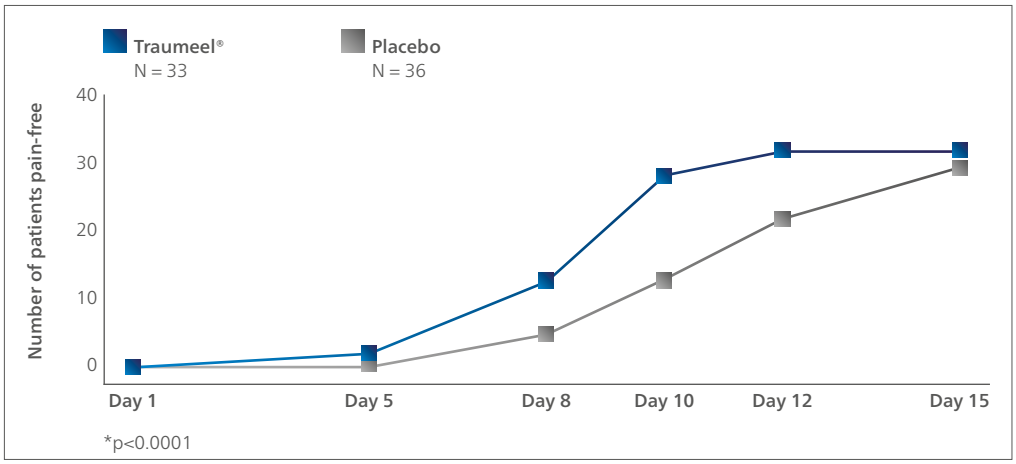


Figure 12 Patients with no pain upon movement within two weeks after beginning therapy with Traumeel® ointment.

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

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	FORMULATION	INDICATION(S)
Randomized, placebo-controlled double-blind study.	Traumeel® ointment.	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 and the 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 13).
- By day 15, pain was reduced by nearly 80% in the Traumeel® group and 63% in the placebo group ($p<0.001$) (Figure 13).
- 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.

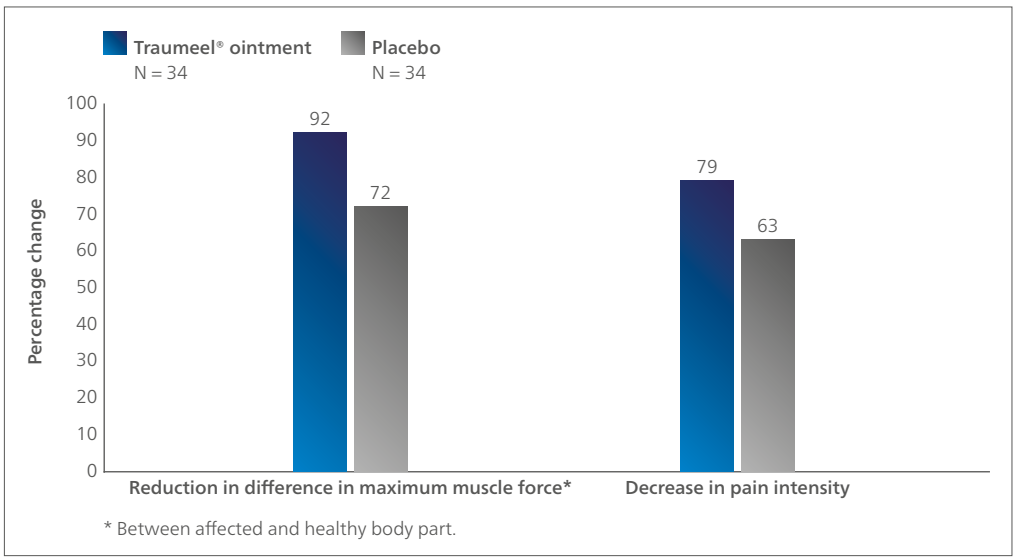


Figure 13 Changes in maximum muscle force and decrease in pain after 15 days of treatment in %.

Conclusion

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

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

Lozada C, del Rio E, Reitberg D, Smith R, Kahn C, Moskowitz RW. A double-blind, randomized, saline-controlled study of the efficacy and safety of co-administered intra-articular injections of Tr14 and Ze14 for treatment of painful osteoarthritis of the knee: The MOZArT trial. *Eur J Integr Med*. 2017:13:54–63.

STUDY DESIGN	FORMULATION	INDICATION(S)
Multi-center, randomized, placebo-controlled double-blind trial.	Traumeel® injection combined with Zeel® T injection.	Moderate-to severe chronic knee osteoarthritis.

Study design

- Patients with moderate-to-severe chronic knee OA were randomized to receive 3 weekly intra-articular (IA) 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).
  - Study visits were at screening/start of wash-out period, start of lead-in period, baseline/randomization/first dose (Day 1), second dose (Day 8), third dose (Day 15), site visits on alternate weeks for 12 weeks, with phone calls to patients in-between visits (every other week).

End points

- Primary endpoint
  - Change in knee pain from Baseline (Day 1, predose) to End-of-Study (Day 99) as measured by the WOMAC* OA Pain Subscore (A) 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)
  - Change in time to walk (50 ft walk test)
  - Consumption of rescue medication
  - Patient and physician global assessments.
- Clinical relevance was assessed, in a *post-hoc* analysis, by comparing treatments with respect to the proportions of patients for whom the improvements from baseline in WOMAC Pain Subscale met or exceeded a Minimum Clinically Important Improvement (MCII). The MCII was set at the highest level (36.6 mm) suggested for 100 mm VAS assessments of knee OA pain.
- 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.

Primary endpoint

- The primary endpoint demonstrated that mean (SD) change in knee pain (mm) from baseline (Day 1, pre-dose) to end-of-study (Day 99) was -32.0 (26.88) in the Traumeel® and Zeel® T and -25.5 (24.08) in the saline group; the difference was statistically significant, favoring Traumeel® and Zeel® T (p=0.0383, 95% CI for difference: -12.40, -0.35).
    - At all visits, mean pain (WOMAC A Pain) decrease was higher in Traumeel® and Zeel® T than in the saline group. Differences between treatment groups were statistically significant (p<0.05) at all visits except Days 8 and 29 (Figure 14).
- In the *post-hoc* analysis, 57/117 (48.7%) patients treated with IA Traumeel® and Zeel® T met the MCII criterion for clinical relevance, compared with 36/111 (32.4%) patients with IA placebo (p=0.0054) (Figure 15).

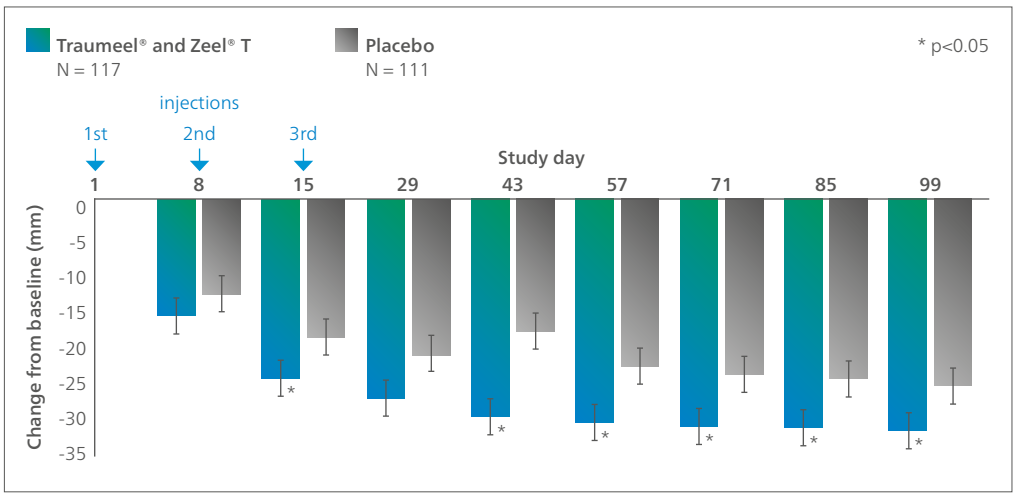


Figure 14 Mean (95% CI) change from baseline in WOMAC A (knee pain subscale) versus study day.

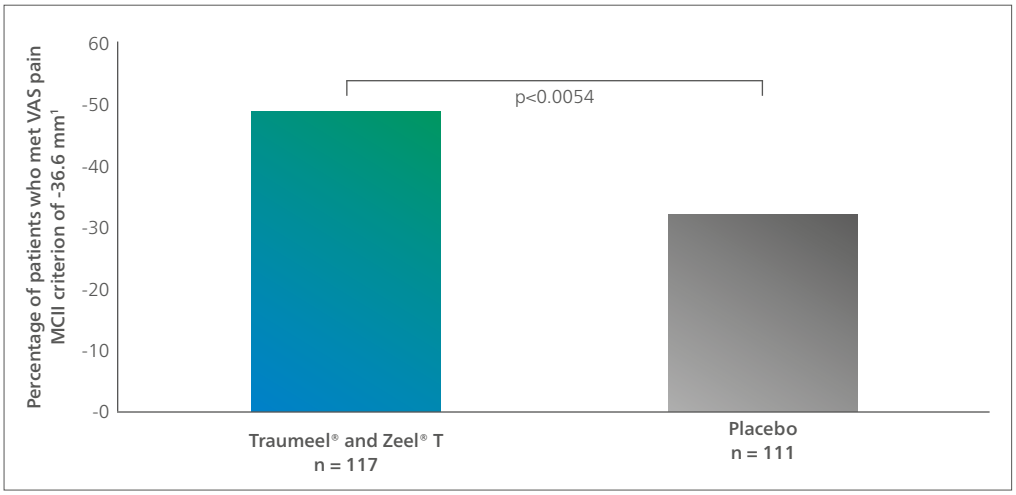


Figure 15 Percentage of patients who met MCII threshold for clinically relevant WOMAC A (Knee Pain Subscale) improvement at end-of-study compared to baseline.

- The statistically normalized (Hedges' g*) efficacy effect sizes for Traumeel® and Zeel® T compared to saline for the WOMAC OA Pain Subscale indicated persistent efficacy over time.
    - These values were comparable or superior to the statistically normalized effect sizes of independently reported standard-of-care IA and oral treatments versus IA placebo treatments published in the meta-analysis by Bannuru et al.

Secondary endpoints

- Stiffness and physical function WOMAC Scores showed greater mean (SD) decreases from baseline to end-of-study visit in Traumeel® and Zeel® T compared with saline but statistical significance was reached at Day 43 only (p= 0.0276).
- Mean (SD) change in pain (VAS) from baseline to end-of-study following an unassisted 50-foot walk test improved significantly for Traumeel® and Zeel® T compared to the saline control (p = 0.0466). Traumeel® and Zeel® T was significantly superior to saline (p<0.05) on all days post-Day 8 (time of 2nd of 3 weekly injections) except Day 29 (p=0.0501) (Figure 16).
- Overall, 102 patients receiving Traumeel® and Zeel® T and 87 in the saline-control group reported taking rescue-medication, with a median number of 23.5 and 46.0 tablets, respectively. No rescue medication was needed by 20 (17.1%) patients receiving Traumeel® and Zeel® T and 13 (11.7%) in the saline-control group.
- Both Patient (PGA) and Physician Global Assessments (PhGA) improved during the course of the study, with greater improvement in patients who received Traumeel® and Zeel® T, with statistical significance seen only in the PhGA at specific study visits (days 29, 71 and 85).

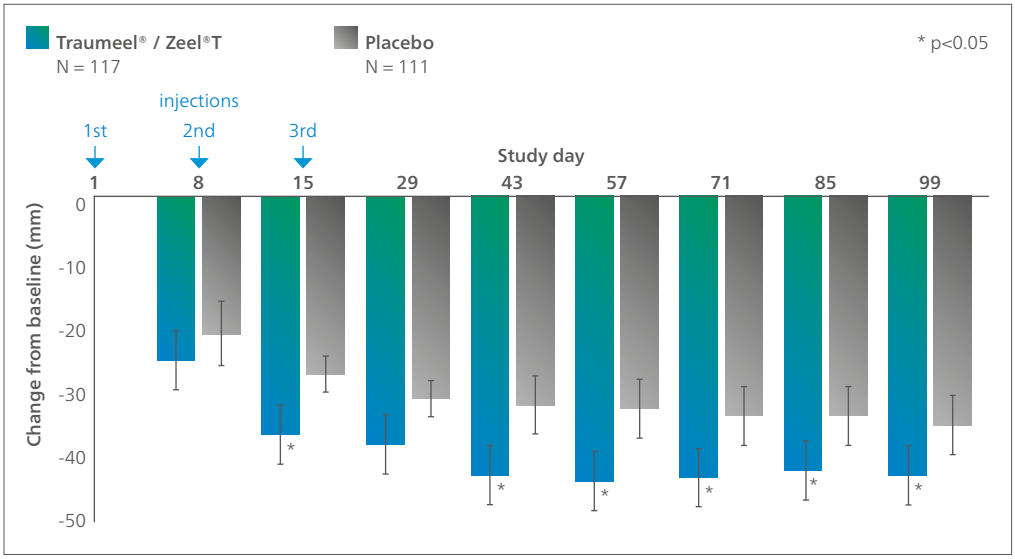


Figure 16 Mean (95% CI) change from baseline in 50 ft walk pain versus study day.

- Treatment groups were similar with regard to AEs, particularly when considering that patients taking Traumeel® and Zeel® T completed the study more often than saline-treated patients.
- The serious ADR rate was well below the targeted 1:30,000 patient-years rate as recommended by the 2011 Consensus Guideline of the Osteoarthritis Research Society International for OA treatments being investigated in randomized clinical trials (RCTs).

Conclusion

- Traumeel® and Zeel® T co-administered intra-articular injections are significantly superior to placebo in reducing knee pain in subjects with moderate-to-severe pain associated with knee osteoarthritis.
- Traumeel® and Zeel® T treatment results in a clinically relevant reduction of pain for patients with osteoarthritis of the knee over a three-month period.
- The pain reduction of Traumeel® and Zeel® T in the MOZArT study is comparable to other intra-articular injection therapies and higher than for oral therapies.
- The co-administration of Traumeel® and Zeel® T is safe and very well tolerated.

NON-RANDOMIZED OBSERVATIONAL STUDIES

Traumeel® compared with conventional therapy in the treatment of injuries

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	FORMULATION	INDICATION(S)
Multi-center, prospective, comparative observational cohort study.	Traumeel® in various forms, e.g. tablets, ointment and injections.	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 17).
- 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.

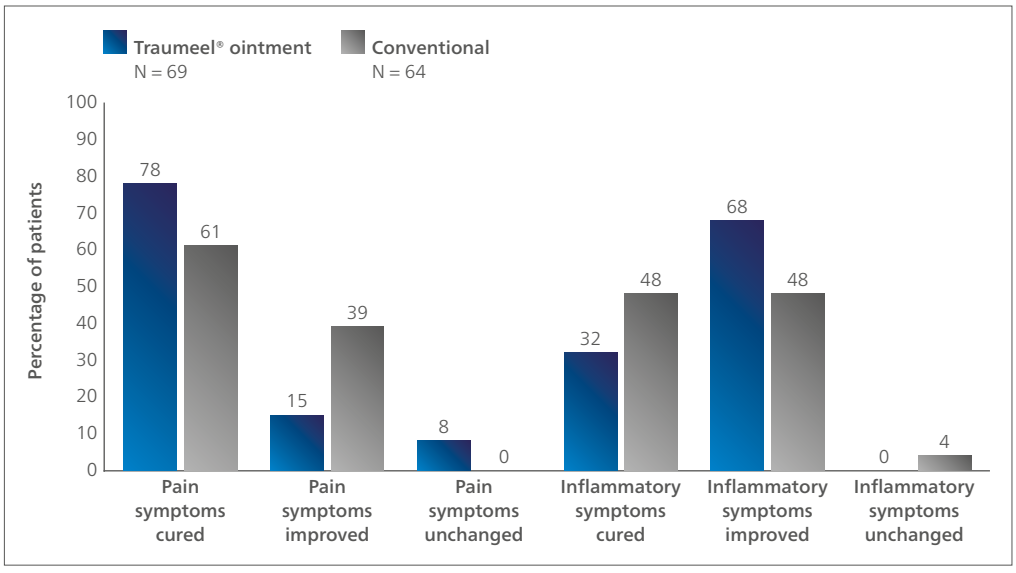


Figure 17 Changes in the principal symptoms of pain and inflammation at the end of the treatment period.

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

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	FORMULATION	INDICATION(S)
Non-randomized, observational study.	Traumeel® ointment.	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%.

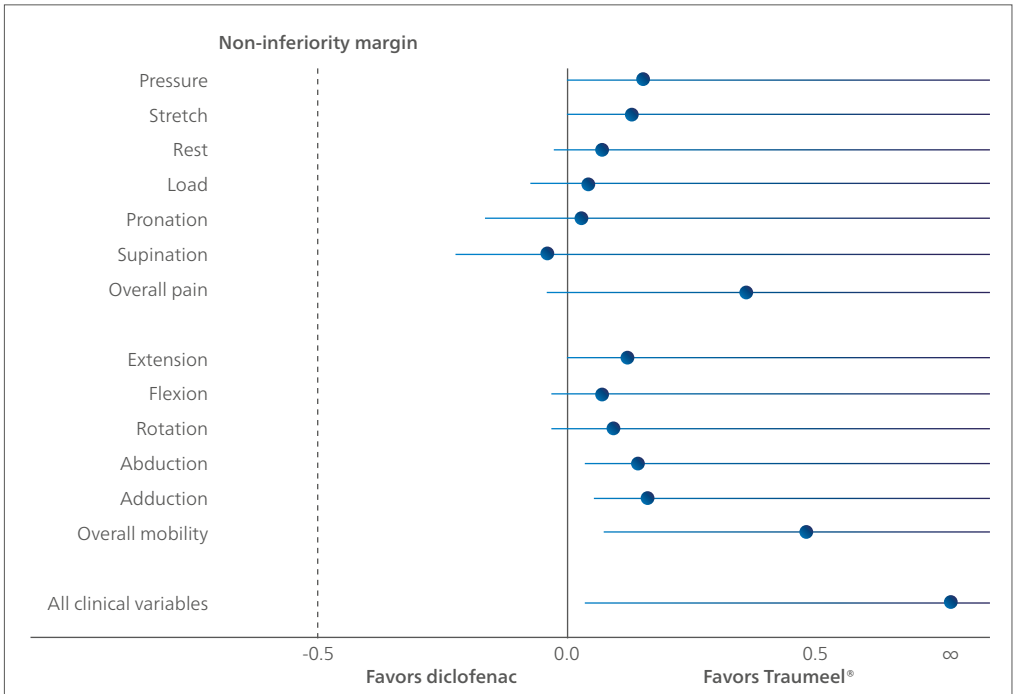
Outcome measures

- 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 18). 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.
- 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.



(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.)

Figure 18 Point estimate and one-sided 95% confidence interval for the difference between scores for Traumeel® and control for all variables.

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

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	FORMULATION	INDICATION(S)
Non-randomized, observational study.	Traumeel® injection.	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 were not 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 19).
- 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 ($p=0.11$).

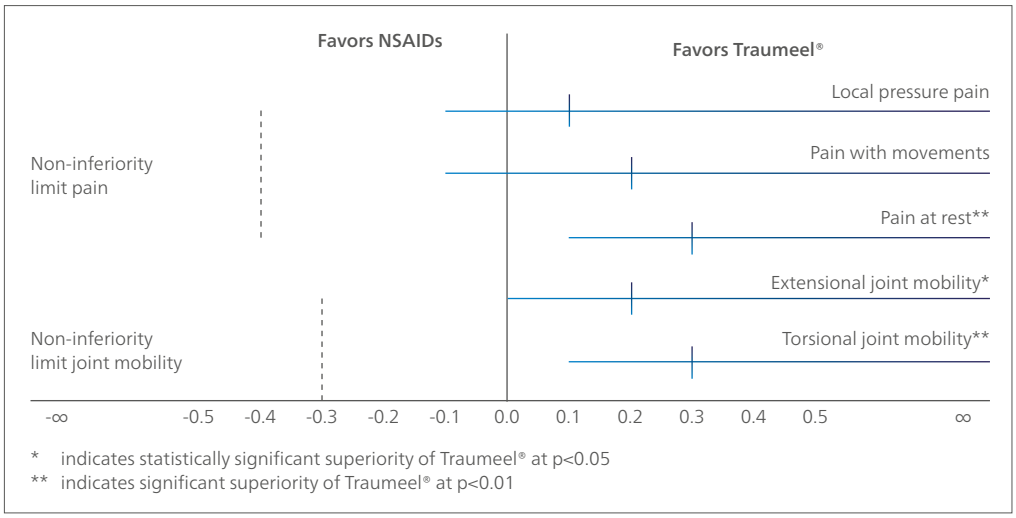


Figure 19 Mean difference with 97.5% confidence interval between symptom scores after two weeks for patients treated with NSAIDs (n=77) and Traumeel® (n=86).

Conclusion

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

SURVEILLANCE STUDIES

Drug surveillance for Traumeel® ointment

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	FORMULATION	INDICATION(S)
Multi-centric, post-marketing drug surveillance.	Traumeel® ointment.	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 20).
- 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).

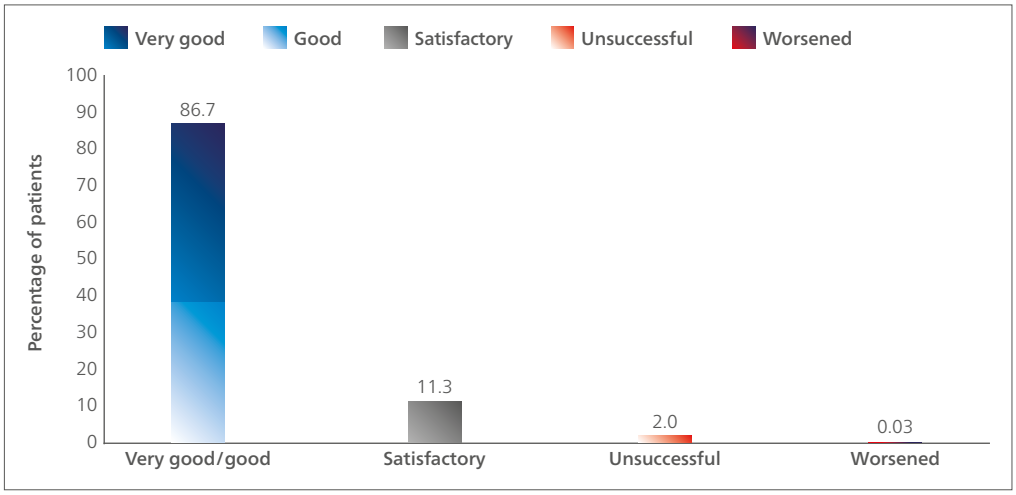


Figure 20 Results of therapy for patients with the biological medication Traumeel® ointment (n=3,422).

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

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	FORMULATION	INDICATION(S)
Multi-centric, drug monitoring trial.	Traumeel® injection.	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 21).
- 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).

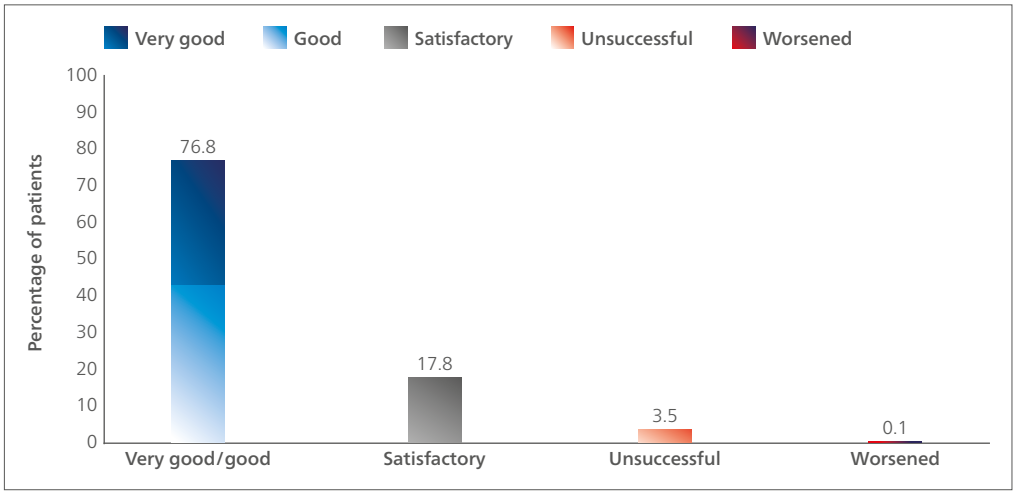


Figure 21 Results of therapy among patients treated with Traumeel® injection (n=3,421).

Conclusions

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

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

STUDY DESIGN	FORMULATION	INDICATION(S)
Multi-center, prospective study.	Traumeel® tablets and drops.	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 22).
- Both oral forms of Traumeel® were well tolerated and no adverse reactions were observed.

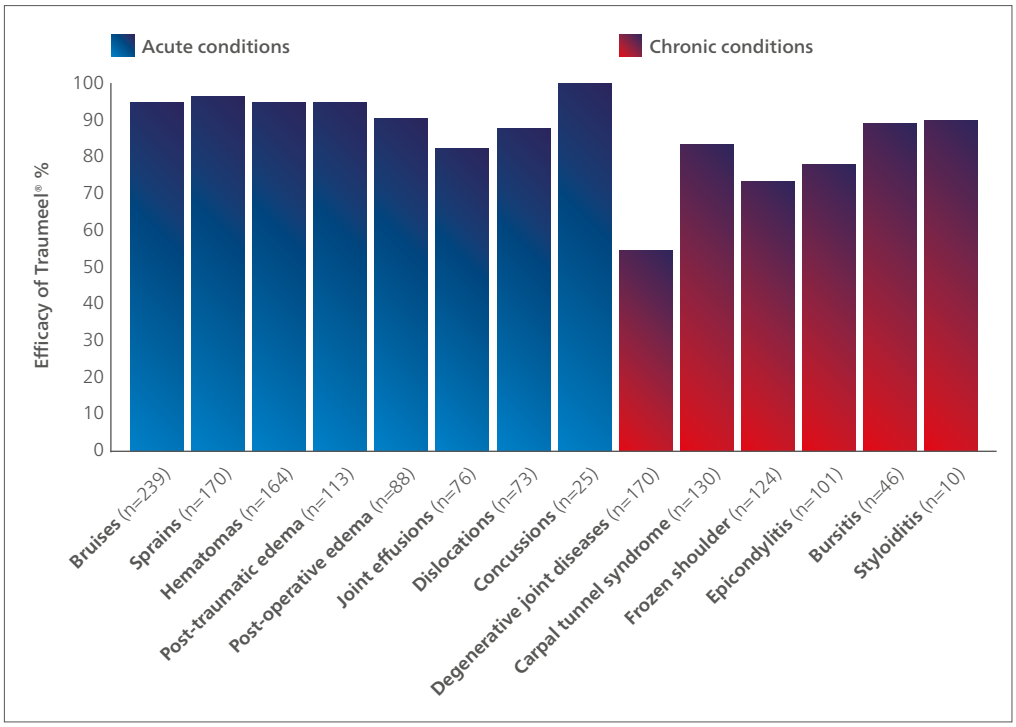


Figure 22 Good to very good efficacy of Traumeel®, in %*.

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

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

STUDY DESIGN	FORMULATION	INDICATION(S)
Observational study.	Traumeel® ointment.	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 23).
- 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.

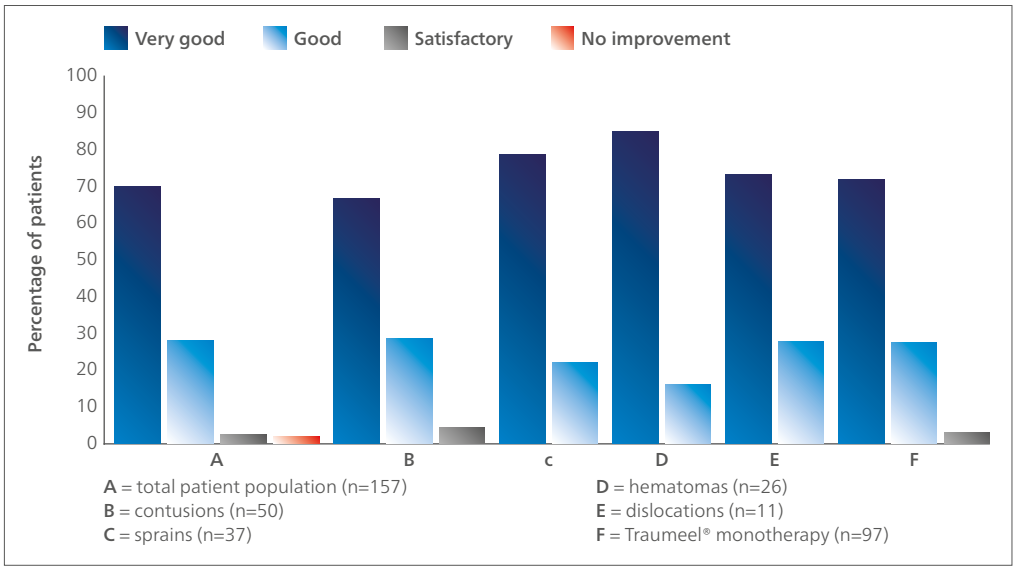


Figure 23 Results of therapy with Traumeel®.

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.

7 CLINICAL SAFETY

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.[Conforti 1997] 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).[Conforti 1997] 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.[Arora 2000] 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.[Arora 2000]

A total of 11 subjects reported 36 adverse events after taking Traumeel®:[Arora 2000]

- 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.[Arora 2000]

> "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."[Arora 2000]

Randomized-controlled trials

In placebo-controlled trials, no adverse effects were reported with either placebo or Traumeel®.[Zell 1998, Böhmer 1992] 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.[González de Vega 2013] In the MOZArT study, treatment groups were similar with regard to adverse events, particularly when considering that patients taking Traumeel® and Zeel® T completed the study more often than saline-treated patients.[Lozada 2017] The serious adverse drug reaction (ADR) rate was well below the targeted 1:30,000 patient-years rate as recommended by the 2011 Consensus Guideline of the Osteoarthritis Research Society International for OA treatments being investigated in randomized clinical trials.[Strand 2011, Lozada 2017]

Tolerability

Post-marketing drug surveillance has shown that tolerability of Traumeel® is good to very good.[Zenner 1992, 1994, 1997]

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.[Zenner 1992]

In 3,446 cases treated with Traumeel® ointment there were only 13 reports of undesired effects that were chronologically associated with topical ointment administration.[Zenner 1994] 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.[Zenner 1997]

Observational studies comparing Traumeel® with conventional treatments for musculoskeletal injury show that the tolerability of Traumeel® is significantly greater compared with conventional treatment.[Birnesser 1994, Schneider 2008]

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.[Birnesser 1994] 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.[Schneider 2008] 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.

In MOZArT, the co-administration of Traumeel® and Zeel® T was safe and very well tolerated.[Lozada 2017]

SAFETY IN CHILDREN

Data in children are limited to one study conducted in 157 children aged 0–12 years, median age 10 years.[Ludwig 2001] 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

Like all medicinal products, this homeopathic medicinal product can cause side effects, although not everybody gets them. **Tablets:** In isolated cases transient skin reactions have been reported. **Solution for Injection:** In isolated cases transient allergic (hypersensitivity) reactions (e.g. skin allergies, redness/swelling at the injection site, even up to anaphylaxis) have been reported. **Ointment:** In isolated cases transient skin reactions have been reported. **Gel:** In isolated cases transient skin reactions (eg. rash, itchiness) have been reported. **Drops:** In isolated cases transient allergic skin reactions have been reported.

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

Tablets, Solution for Injection, Gel, Drops: 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). **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. As this product contains Echinacea, individual evaluation is recommended before prescribing this product in patients with immune system dysfunction, e.g. cases of progressive systemic disorders, autoimmune diseases, immunodeficiencies, immunosuppression and diseases of the white blood cell system. **Solution for Injection:** As this product contains Echinacea, individual evaluation is recommended before prescribing this product in patients with immune system dysfunction, e.g. cases of progressive systemic disorders, autoimmune diseases, immunodeficiencies, immunosuppression and diseases of the white blood cell system. **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. **Drops:** This medicinal product contains 35 vol.-% ethanol (alcohol). As this product contains Echinacea, individual evaluation is recommended before prescribing this product in patients with immune system dysfunction, e.g. cases of progressive systemic disorders, autoimmune diseases, immunodeficiencies, immunosuppression and diseases of the white blood cell system.

Effects on ability to drive and use machines

Tablets, Solution for Injection: 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. **Drops:** This medicinal product has no or negligible influence on the ability to drive and use machines.

PREGNANCY AND LACTATION

For this product no clinical data on pregnancy and lactation are available. Homeopathic dilutions of the substances present in this medicinal product are not known to be harmful during pregnancy and lactation. No adverse effects have so far been reported.

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.

8 USE IN CLINICAL PRACTICE

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[FDA MedWatch]

- 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[FDA MedWatch]

- 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.[FDA MedWatch]

Drugs diclofenac can interact with:

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.[FDA MedWatch]

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.[González de Vega 2013]

In addition, the 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).[Lozada 2017] The significant reduction in pain observed with Traumeel® and 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. The pain reduction of Traumeel® and Zeel® T in the MOZArT study is comparable to other intra-articular injection therapies and higher than for oral therapies.[Lozada 2017]

In observational cohort studies Traumeel® has shown significantly better tolerance compared with NSAIDs.[Birnesser 2004, Schneider 2008] 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.[Zenner 1992, 1994, 1997]

Therapeutic algorithm – management of musculoskeletal injury

In view of the results from TAASS, the established evidence base, and new data on inflammation resolution, the authors of a recent publications by Wolfarth et al. suggest a revised therapeutic algorithm in primary care for acute, sub-acute or acute on chronic pain/swelling of presumed musculoskeletal origin.[Wolfarth 2022] The algorithm is particularly relevant in patients with mild-to-moderate symptoms where there is a desire to avoid or complement the effects of NSAIDs. Traumeel®, a multitarget agent, is considered part of the general armamentarium to manage these conditions.[Wolfarth 2022]

GUIDELINE RECOMMENDATIONS IN SPORTS MEDICINE

The growing evidence base for the use of Traumeel® is leading to increasing recognition among the medical community and inclusion in consensus statements and guidelines.[Bisciotti 2018, Fernandes Jaen 2016, Del Valle Soto 2013]

Italian consensus conference (CC) on guidelines on conservative treatment on lower limb muscle injuries in athlete:[Bisciotti 2018]

- The CC presented a clear overview of the state of the art of pharmacological and instrumental therapy concerning muscle injury.
- The CC considered Traumeel®, marketed in Italy as ointment, tablets, drops and ampoules for injection.
- It is noted that in the literature, there are randomized controlled trials that show its efficacy in the reduction of pain and swelling following muscle injuries.
- They also noted that Traumeel® has proven to be well-tolerated with little adverse effects.
- The CC 'hopes that further evidence in the future will confirm its therapeutic validity.'

A consensus document issued by the Spanish Federation of Sports Medicine (FEMEDE) on injectable therapies aims to improve patient quality of care and assist in making therapeutic decisions:[Del Valle Soto 2013]

- The level of scientific evidence that supports the use of bioregulatory drugs (particularly Traumeel®) can be considered acceptable and there is a growing literature supporting use.
- Therefore, injectable biologic therapies are an alternative in the treatment of sports injuries and their effects are comparable to those of other drugs and usually have no side effects.
- Components of bioregulatory therapy can modulate inflammation and injury symptoms, they are analgesic, stimulate healing and may have hemostatic effects contributing to eliminate edema and venous stasis.
- Their ultimate goal is to restore the normal functioning of the regulatory mechanisms.
- The choice of the injectable route will depend on the type of pathology, the injury severity, the patient's general condition and also the clinical experience of the prescribing physician.
- These injectable therapies can be administered alone, associated with each other or with other medicines or techniques.
- The increasing level of scientific evidence demonstrates that bioregulatory therapies in the treatment of sports injuries and their effects are comparable to those of other drugs, including NSAIDs, and have a favorable safety profile.

Spanish Consensus Statement: The Treatment of Muscle Tears in Sport:[Fernandes Jaen 2016]

- Experts from the Spanish Society for Sports Traumatology and FEMEDE developed a consensus document to consider the most appropriate actions to be taken when treating muscle tears, based on proven scientific data.
- The sports traumatology experts considered four differentiated phases during muscle repair: inflammatory; degenerative and vascularization; cell-stimulating, proliferative, and fibrotic; and the remodeling phase.
- The recommendations concluded that anti-inflammatory administration must be avoided since it greatly affects biochemical reactions present in inflammation, thus causing muscle recovery to slow down

- Regulating inflammatory mechanisms, without inhibiting these from the early stages of the recovery period, is recommended
- Administration of inflammatory bioregulators (such as Traumeel®) regulates any response, promoting an anti-inflammatory process activation.

Use in elite sports

Traumeel® is widely used among the sports specialists, including the Olympic and world champions' physicians, and is mentioned in many textbooks and guidelines in this field.[Bisciotti 2018, Del Valle Soto 2013, Muller-Wohlfahrt 2018, Muller Wolfarth 2021]

An important point, particularly for users, recommenders and prescribers of Traumeel® to athletes and sports professionals, is that none of the components of Traumeel® are considered doping agents.

- Traumeel® is not listed on the World Anti-Doping Agency (WADA) list of banned products.[WADA 2022]
- In Germany, Traumeel® is listed as "may be used" on the National Anti-Doping Agency (NADA) list.[NADA 2022]

For this reason, in sports medicine, Traumeel® is widely used in the treatment of trauma and inflammation of joints and soft tissues.

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
- Drops.

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.
Drops: In general, 10 drops 3 times daily.

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: Active ingredients: Achillea millefolium D3 15.0 mg; Aconitum napellus D3 30.0 mg; Atropa belladonna D4 75.0 mg; Hepar sulfuris D8 30.0 mg; Matricaria recutita D3 24.0 mg; Mercurius solubilis Hahnemanni D8 30.0 mg; Symphytum officinale D8 24.0 mg; Bellis perennis D2 6.0 mg; Calendula officinalis D2 15.0 mg; Echinacea D2 6.0 mg; Echinacea purpurea D2 6.0 mg; Hamamelis virginiana D2 15.0 mg; Hypericum perforatum D2 3.0 mg; Arnica montana D2 15.0 mg. Excipients: Lactose monohydrate 6.0 mg; Magnesium stearate 1.5 mg. Contains lactose! Please see package insert!
Solution for Injection: 1 ampoule of 2.2 ml (= 2.2 g) contains: Active ingredients: Achillea millefolium D3 2.20 mg; Matricaria recutita D3 2.20 mg; Symphytum officinale D6 2.20 mg; Aconitum napellus D2 1.32 mg; Atropa belladonna D2 2.20 mg; Bellis perennis D2 1.10 mg; Calendula officinalis D2 2.20 mg; Echinacea D2 0.55 mg; Echinacea purpurea D2 0.55 mg; Hypericum perforatum D2 0.66 mg; Hepar sulfuris D6 2.20 mg; Mercurius solubilis Hahnemanni D6 1.10 mg; Hamamelis virginiana D1 0.22 mg; Arnica montana D2 2.20 mg. Excipients: Sodium chloride 19.4 mg, Water for injections 2179.1 mg.
Ointment: 100 g containing: Active ingredients: Achillea millefolium D4 0.090 g; Aconitum napellus D4 0.050 g; Arnica montana D4 1.500 g; Atropa belladonna D4 0.050 g; Bellis perennis D4 0.100 g; Calendula officinalis D4 0.450 g; Echinacea D4 0.150 g; Echinacea purpurea D4 0.150 g; Hamamelis virginiana D4 0.450 g; Hepar sulfuris D6 0.025 g; Hypericum perforatum D6 0.090 g; Matricaria recutita D4 0.150 g; Mercurius solubilis Hahnemanni D6 0.040 g; Symphytum officinale D4 0.100 g. Excipients: Paraffin, liquid 9.342 g; Cetostearyl alcohol (type A), emulsifying 8.007 g; Paraffin, white soft 9.342 g; Water, purified 60.579 g; Ethanol (96%) 9.335 g; Preserved with 12.7 vol.-% alcohol.

Gel: 100 g containing: Active ingredients: Achillea millefolium D0 0.090 g; Aconitum napellus D1 0.050 g; Arnica montana D3 1.500 g; Atropa belladonna D1 0.050 g; Bellis perennis D0 0.100 g; Calendula officinalis D0 0.450 g; Echinacea D0 0.150 g; Echinacea purpurea D0 0.150 g; Hamamelis virginiana D0 0.450 g; Hepar sulfuris D6 0.025 g; Hypericum perforatum D6 0.090 g; Matricaria recutita D0 0.150 g; Mercurius solubilis Hahnemanni D6 0.040 g; Symphytum officinale D4 0.100 g. Excipients: Water, purified 74.652 g; Ethanol (96%) 18.653 g; Carbomers (Carbopol 980NF) 1.000 g; Sodium hydroxide solution 18% (m/m) 2.300 g; Contains 24.4 vol.-% alcohol. Purified water, ethanol 96% (V/V), carbomers, sodium hydroxide solution 18% m/m.
Drops: 100 g containing: Active ingredients: Aconitum napellus D3 10.0 g; Atropa belladonna D4 25.0 g; Symphytum officinale D8 8.0 g; Achillea millefolium D3 5.0 g; Calendula officinalis D2 5.0 g; Echinacea D2 2.0 g; Echinacea purpurea D2 2.0 g; Hamamelis virginiana D2 5.0 g; Hypericum perforatum D2 1.0 g; Matricaria recutita D3 8.0 g; Hepar sulfuris D8 10.0 g; Mercurius solubilis Hahnemanni D8 10.0 g; Arnica montana D2 5.0 g; Bellis perennis D2 2.0 g. Excipients: Water, purified 2.0 g; Contains 35 vol.-% alcohol.

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.
Drops: Drop bottles containing 30 and 100 ml.

9 SUMMARY

- Traumeel® is a multitarget, multicomponent medication that supports inflammation resolution, accelerates the healing process and provides sustained recovery from injury. [St Laurent 2017 & 2021, Jordan 2021, González de Vega 2013, Birnesser 2004, Schneider 2005, Muders 2016, 2017, Cesnulevicius 2011]
- Traumeel® contains 14 natural ingredients working together to deliver effective and well tolerated relief of inflammation symptoms.[Cesnulevicius 2011, Lussignoli 1999]
- 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. According to the research, Traumeel® regulates the inflammatory process in different organs and tissues, including acute, chronic, and degenerative disorders of the musculoskeletal system.
- Traumeel® has a different mode of action to conventional anti-inflammatory drugs.[St Laurent 2017 & 2021, Jordan 2021]
- Traumeel® has a well-established efficacy and safety profile:
  - 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.[González 2013, Böhmer 1992, Zell 1989]
  - 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.[Zenner 1992, 1994, 1997, Schneider 2008]
  - 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. A treatment algorithm has been developed to assist clinicians in the appropriate utilization of Traumeel® in clinical practice. Sporting institutions in Italy, Spain and Germany acknowledge Traumeel's efficacy and safety in their respective consensus guidelines or recommendations.
  - The MOZArT (Management of Osteoarthritis of the Knee with Zeel And Traumeel Injections) study, a large randomized controlled trial, demonstrated that Traumeel® and Zeel® T co-administered intra-articular injections are significantly superior to placebo in reducing knee pain in subjects with moderate-to-severe pain associated with knee osteoarthritis.[Lozada 2017]
  - The pain reduction of Traumeel® and Zeel® T in the MOZArT study is comparable to other intra-articular injection therapies and higher than for oral therapies.[Lozada 2017]
  - Tolerability of Traumeel® has been demonstrated to be significantly greater than with conventional treatments.
  - Safety studies have indicated that Traumeel® is unlikely to interfere with antimicrobial first defences, the normal homeostatic process, kidney function or liver function.

- Post-marketing surveillance has demonstrated very good tolerability for Traumeel® formulations (significantly greater than with conventional treatments) with very few adverse effects.[Zenner 1992, 1994, 1997]
- Traumeel® is suitable for patients requiring first-line treatment for musculoskeletal injuries and inflammation. It may be particularly suitable for patients who are unable to tolerate conventional anti-inflammatory medication, or for those in whom such treatment is contraindicated.[Arora 2000, Zenner 1992, 1994, 1997]
- Investigation of the efficacy and place in therapy of Traumeel® is ongoing, with further randomized controlled trials underway.

- Traumeel® is registered as a homeopathic medicinal product for the treatment of musculoskeletal injuries and inflammation.

TRAUMEEL® HAS A WELL-ESTABLISHED EFFICACY, EFFECTIVENESS AND SAFETY PROFILE

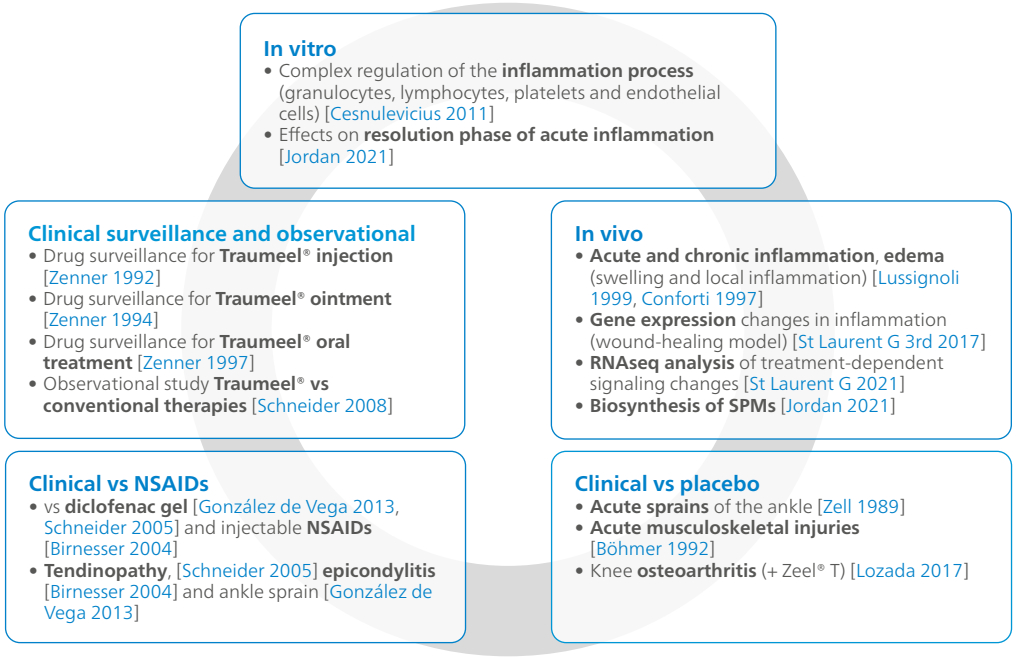


Figure 24 Traumeel® efficacy, effectiveness and safety profile

- Birnesser H, Oberbaum M, Klein P, Weiser M. The homeopathic preparation Traumeel® S compared with NSAIDs for symptomatic treatment of epicondylitis. *J Musculoskelet Res.* 2004;8(2 & 3):119–128.
- Böhmer D, Ambrus P. Treatment of sports injuries with Traumeel ointment: a controlled double-blind study. *Biol Ther.* 1992;10:290–300.
- Cesnulevicius K. The bioregulatory approach to work-related musculoskeletal disorders: using the multicomponent ultra low-dose medication Traumeel to target the multiple pathophysiological processes of the disease. *Altern Ther Health Med.* 2011;17(suppl 2):S8–S17.
- Conforti A, Bertani S, Metelmann H, et al. Experimental studies on the anti-inflammatory activity of a homeopathic preparation. *Biomed Ther.* 1997;15(1):28–31.
- 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, randomised, blinded, controlled and non-inferiority trial. *Int J Clin Pract.* 2013;67(10):979–989.
- Jordan PM, van Goethem E, Müller AM, Hemmer K et al. The Natural Combination Medicine Traumeel (Tr14) Improves Resolution of Inflammation by Promoting the Biosynthesis of Specialized Pro-Resolving Mediators. *Pharmaceuticals (Basel).* 2021 Nov 3;14(11):1123.
- Lozada CJ, del Rio E, Reitberg DP, et al. A double-blind, randomized, saline-controlled study of the efficacy and safety of co-administered intra-articular injections of Tr14 and Ze14 for treatment of painful osteoarthritis of the knee: the MOZArT trial. *Eur J Integr Med.* 2017;13:54–63.
- Lussignoli S, Bertani S, Metelmann H, et al. Effect of Traumeel S, a homeopathic formulation, on blood-induced inflammation in rats. *Complement Ther Med.* 1999;7(4):225–230.
- St Laurent G et al. RNAseq Analysis of Treatment-dependent Signaling Changes During Infammation in a Mouse Cutaneous Wound Healing Model. *BMC Genomics.* 2021;22(1):854. Published 2021 Nov 25.
- St Laurent G 3rd, Seilheimer B, Tackett M, et al. Deep sequencing transcriptome analysis of murine wound healing: effects of a multicomponent, multitarget natural product therapy-Tr14. *Front Mol Biosci.* 2017;4:57.
- 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):22–7. doi: 10.1016/j.ctim.2007.04.004. Epub 2007 Jul 12.
- Schneider C, Klein P, Stolt P, Oberbaum M. A homeopathic ointment preparation compared with 1% diclofenac gel for acute symptomatic treatment of tendinopathy. *Explor J Sci Heal.* 2005;1(6):446–452.
- Zell J, Connert WD, Mau J, Feuerstake G. Treatment of acute sprains of the ankle: a controlled double-blind trial to test the effectiveness of a homeopathic ointment. *Biol Ther.* 1989;7(1):1–6.
- 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.
- 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.
- Zenner S, Weiser M. Oral treatment of traumatic, inflammatory, and degenerative conditions with a homeopathic remedy. *Biomed Ther.* 1997;XV(1):22–26.

10 TRAUMEEL® CLINICAL STUDIES

- 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.
- Böhmer D, Ambrus P. Treatment of sports injuries with Traumeel® ointment: a controlled double-blind study. *Biol Ther.* 1992;X(4):290–300.
- 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.
- Lozada C, del Rio E, Reitberg D, Smith R, Kahn C, Moskowitz RW. A double-blind, randomized, saline-controlled study of the efficacy and safety of co-administered intra-articular injections of Tr14 and Ze14 for treatment of painful osteoarthritis of the knee: The MOZArT trial. *Eur J Integr Med.* 2017:13:54–63.
- Ludwig J, Weiser M. Treating pediatric trauma with a homeopathic ointment. *J Biomed Ther.* 2001; Summer: 8–11.
- 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. doi:10.1016/j.explore.2005.08.010.
- 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. doi:10.1016/j.ctim.2007.04.004.
- 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.* 1989;VII(1):1–6.
- 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):301–10.
- Zenner S, Metelmann H. Therapy experience with a homeopathic ointment: results of drug surveillance conducted on 3,422 patients. *Biol Ther.* 1994;XII(3):204–11.
- Zenner S, Weiser M. Oral treatment of traumatic, inflammatory, and degenerative conditions with a homeopathic remedy. *Biol Ther.* 1997;XV(1):22–6.

11 REFERENCES

- Adatia A, Rainsford KD, Kean WF. Osteoarthritis of the knee and hip. Part I: aetiology and pathogenesis as a basis for pharmacotherapy. *J Pharm Pharmacol.* 2012;64(5):617–625. doi:10.1111/j.2042-7158.2012.01458.x
- Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum.* 1986 ;29(8):1039–1049. doi:10.1002/art.1780290816
- Amoako AO, Pujalte GG. Osteoarthritis in young, active, and athletic individuals. Clin Med Insights *Arthritis Musculoskelet Disord.* 2014;7:27–32. Published 2014 May 22. doi:10.4137/CMAMD.S14386
- Arora S, Harris T, Scherer C. Clinical safety of a homeopathic preparation. *Biomed Ther.* 2000;XVIII(2):222–225.
- Arroll B, Goodyear-Smith F. Corticosteroid injections for osteoarthritis of the knee: meta-analysis. *BMJ.* 2004;328(7444):869. doi:10.1136/bmj.38039.573970.7C
- Arden N, Newitt MC: Osteoarthritis: Epidemiology. *Best Pract Res Clin Rheumatol.* 2006;20(1):3–25. doi:10.1016/j.berh.2005.09.007
- Bahr R, Krosshaug T. Understanding injury mechanisms: a key component of preventing injuries in sport. *Br J Sports Med.* 2005;39(6):324–329. doi:10.1136/bjsm.2005.018341
- Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. *Ann Intern Med.* 2015;162(1):46-54. doi:10.7326/M14-1231
- Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage.* 2019;27(11):1578–1589. doi:10.1016/j.joca.2019.06.011
- Belikan P, Nauth L, Färber LC, et al. Intramuscular injection of combined calf blood compound (CFC) and homeopathic drug Tr14 accelerates muscle regeneration in vivo. *Int J Mol Sci.* 2020;21(6):2112. Published 2020 Mar 19. doi:10.3390/ijms21062112
- Berg JM, Tymoczko JL, Stryer L. Gene expression is the transformation of DNA information into functional molecules. *Biochemistry.* 5th ed. W. H. Freeman; 2002. Publishing, New York. Available from: https://biokamikazi.files.wordpress.com/2013/10/biochemistry-stryer-5th-ed.pdf [Accessed September 29, 2020]
- Birnesser H, Oberbaum M, Klein P, Weiser M. The homeopathic preparation Traumeel® S compared with NSAIDs for symptomatic treatment of epicondylitis. *J Musculosekeletal Research.* 2004;8(2–3):119–128.
- Bisciotti GN, Volpi P, Amato M, et al. Italian consensus conference on guidelines for conservative treatment on lower limb muscle injuries in athlete. *BMJ Open Sport Exerc Med.* 2018;4:e000323. doi:10.1136/bmjsem-2017-000323
- Böhmer S, Ambrus P. Treatment of sports injuries with Traumeel® ointment: a controlled double-blind study. *Biol Ther.* 1992;X(4):290–300.
- Bonnet CS, Walsh DA. Osteoarthritis, angiogenesis and inflammation. *Rheumatology. (Oxford)* 2005;44(1):7–16.
- Braun HJ, Gold GE. Diagnosis of osteoarthritis: imaging. *Bone.* 2012;51(2):278–288. doi:10.1016/j.bone.2011.11.019
- Brumitt J, Cuddeford T. Current concepts of muscle and tendon adaptation to strength and conditioning. *Int J Sports Phys Ther.* 2015;10(6):748–759.

- Cash JL, White GE, Greaves DR. Chapter 17 Zymosan-Induced Peritonitis as a Simple Experimental System for the Study of Inflammation. In: *Methods in Enzymology.* Vol 461. Academic Press; 2009:379–396. doi:10.1016/S0076-6879(09)05417-2
- Cesnulevicius K. The bioregulatory approach to work-related musculoskeletal disorders: using the multicomponent ultra low-dose medication Traumeel to target the multiple pathophysiological processes of the disease. *Altern Ther Health Med.* 2011;17(suppl 2):S8–S17
- Cheng J, Abdi S. Complications of joint, tendon, and muscle injections. *Tech Reg Anesth Pain Manag.* 2007;11(3):141–147. doi:10.1053/j.trap.2007.05.006
- Collins M, Raleigh SM. Genetic risk factors for musculoskeletal soft tissue injuries. *Med Sport Sci.* 2009;54:136–149. doi:10.1159/000235701
- Conforti A, Bertani S, Metelmann H, Chirumbolo S, Lussignoli S, Bellavite P. Experimental studies on the anti-inflammatory activity of a homeopathic preparation. *Biomed Ther.* 1997;XV(1):28–31.
- Das R, Deshmukh J, Asif K, Sindhura H, Devarathanamma MV, Jyothi L. Comparative evaluation of analgesic and anti-inflammatory efficacy of ibuprofen and traumeel after periodontal flap surgery: A randomized triple-blind clinical trial. *J Indian Soc Periodontol.* 2019;23(6):549–553. doi:10.4103/jisp.jisp_85_19
- Debnath M, Prasad GBKS, Bisen PS. Molecular Diagnostics: Promises and Possibilities. Springer Netherlands; 2010. doi:10.1007/978-90-481-3261-4
- Del Valle Soto M, Díaz JF, Marqueta PM, et al. Consensus on use of parenteral therapy in sports. Use of homeopathic medication, biological and bioregulatory therapy. Document of consensus of the Spanish Federation of Sports Medicine. *Arch Med Deporte.* 2013;30(1):8–13.
- Demidova-Rice TN, Hamblin MR, Herman IM. Acute and impaired wound healing: pathophysiology and current methods for drug delivery, part 1: normal and chronic wounds: biology, causes, and approaches to care. *Adv Skin Wound Care.* 2012;25(7):304–314. doi:10.1097/01.ASW.0000416006.55218.d0
- De Oliveira S, Rosowski EE, Huttenlocher A. Neutrophil migration in infection and wound repair: going forward in reverse. *Nat Rev Immunol.* 2016;16(6):378–391. doi:10.1038/nri.2016.49
- Doherty C, Delahunt E, Caulfield B, Hertel J, Ryan J, Bleakley C. The incidence and prevalence of ankle sprain injury: a systematic review and meta-analysis of prospective epidemiological studies. *Sports Med.* 2014;44(1):123–140. doi:10.1007/s40279-013-0102-5
- Felson DT. Developments in the clinical understanding of osteoarthritis. *Arthritis Res Ther.* 2009;11(1):203. doi:10.1186/ar2531
- Feehan KT, Gilroy DW. Is resolution the end of inflammation? *Trends Mol Med.* 2019;25(3):198–214. doi:10.1016/j.molmed.2019.01.006
- Fernandes JC, Martel-Pelletier J, Pelletier JP. The role of cytokines in osteoarthritis pathophysiology. *Biorheology.* 2002;39(1-2):237–246.
- Fernandez-Jaén TF, Rey GÁ, Cuesta JA, et al. Spanish Consensus Statement: The Treatment of Muscle Tears in Sport. *Orthop J Sports Med.* 2016;3(12):2325967115622434. Published 2016 Feb 4. doi:10.1177/2325967115622434
- Food and Drug Administration (FDA) MedWatch Medical Product Safety Information. Available from: https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program/medical-product-safety-information [Accessed 15 June 2022]
- Friel NA, Chu CR. The role of ACL injury in the development of posttraumatic knee osteoarthritis. *Clin Sports Med.* 2013;32(1):1–12. doi:10.1016/j.csm.2012.08.017
- Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. *Arthritis Rheum.* 1980 Feb;23(2):137–145. doi:10.1002/art.1780230202

- Fullerton JN, Gilroy DW. Resolution of inflammation: a new therapeutic frontier. *Nat Rev Drug Discov.* 2016;15(8):551–567. doi:10.1038/nrd.2016.39
- González de Vega C, Speed C, Wolfarth B, Gonzalez 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
- Gribble PA, Bleakley CM, Caulfield BM, et al. Evidence review for the 2016 International Ankle Consortium consensus statement on the prevalence, impact and long-term consequences of lateral ankle sprains. *Br J Sports Med.* 2016;50(24):1496–1505. doi:10.1136/bjsports-2016-096189
- Jones HR, Robb CT, Perretti M, Rossi AG. The role of neutrophils in inflammation resolution. *Semin Immunol.* 2016;28(2):137–145. doi:10.1016/j.smim.2016.03.007
- Haeggstrom JZ. Leukotriene A4 hydrolase/aminopeptidase, the gatekeeper of chemotactic leukotriene B4 biosynthesis. *J Biol Chem.* 2004;279(49):50639–42. doi:10.1074/jbc.R400027200
- Haseeb A, Haqqi TM. Immunopathogenesis of osteoarthritis. *Clin Immunol.* 2013 Mar;146(3):185–196. doi:10.1016/j.clim.2012.12.011
- Helei VM, Zhero NI, Helei NI, Kryvanich VV. Choice of the treatment method of the inflammatory process in the alveolar tooth socket. *Wiad Lek.* 2019;72(10):1957–1960.
- Heine H, Schmolz M. Induction of the immunological bystander reaction by plant extracts. *Biomed Ther.* 1998;XVI(3):224–226.
- Heine H, Andrä F. Zum antiinflammatorischen Wirkmechanismus eines Antihomotoxikum compositum [The anti-inflammatory action mechanism of an antihomotoxic composita remedy]. *Ärztezeit f Naturheilverfahrenn.* 2002;43(2):96–104.
- Heng MC. Wound healing in adult skin: aiming for perfect regeneration. *Int J Dermatol.* 2011;50(9):1058–1066. doi:10.1111/j.1365-4632.2011.04940.x
- Hsu JR, Mir H, Wally MK, Seymour RB; Orthopaedic Trauma Association Musculoskeletal Pain Task Force. Clinical Practice Guidelines for Pain Management in Acute Musculoskeletal Injury. *J Orthop Trauma.* 2019;33(5):e158-e182. doi:10.1097/BOT.0000000000001430
- Irby A, Gutierrez J, Chamberlin C, Thomas SJ, Rosen AB. Clinical management of tendinopathy: A systematic review of systematic reviews evaluating the effectiveness of tendinopathy treatments. *Scand J Med Sci Sports.* 2020; 30: 1810–1826. https://doi.org/10.1111/sms.13734
- Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P et al; Standing Committee for International Clinical Studies Including Therapeutic Trials ESCISIT. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis.* 2003 Dec;62(12):1145–1155. doi:10.1136/ard.2003.011742
- Jordan PM, van Goethem E, Müller AM, Hemmer K et al. The Natural Combination Medicine Traumeel (Tr14) Improves Resolution of Inflammation by Promoting the Biosynthesis of Specialized Pro-Resolving Mediators. *Pharmaceuticals (Basel).* 2021 Nov 3;14(11):1123.
- Kahl OG. The Dictionary of Genomics, Transcriptomics and Proteomics, 4 Volume Set 5th ed.; 2015.
- Kaux JF, Forthomme B, Goff CL, Crielaard JM, Croisier JL. Current opinions on tendinopathy. *J Sports Sci Med.* 2011;10(2):238–253. Published 2011 Jun 1.
- Kawabata A. Prostaglandin E2 and pain--an update. *Biol Pharm Bull.* 2011;34(8):1170–1173. doi:10.1248/bpb.34.1170
- Kirchner M, Marshall D. A double-blind randomized controlled trial comparing alternate forms of high molecular weight hyaluronan for the treatment of osteoarthritis of the knee. *Osteoarthritis Cartilage.* 2006;14(2):154–162. doi:10.1016/j.joca.2005.09.003

- Kompel AJ, Roemer FW, Murakami AM, Diaz LE, Crema MD, Guermazi A. Intra-articular Corticosteroid Injections in the Hip and Knee: Perhaps Not as Safe as We Thought? *Radiology.* 2019;293(3):656-663. doi:10.1148/radiol.2019190341
- Langendorf EK, Klein A, Rommens PM, Drees P, Ritz U, Mattyasovszky SG. Calf Blood Compound (CFC) and Homeopathic Drug Induce Differentiation of Primary Human Skeletal Muscle Cells. *Int J Sports Med.* 2019;40(12):803–809. doi:10.1055/a-0915-2306
- Lohmander LS, Englund PM, Dahl LL, Roos EM. The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis. *Am J Sports Med.* 2007;35(10):1756–1769. doi:10.1177/0363546507307396
- Loynes CA, Lee JA, Robertson AL, et al. PGE_2 production at sites of tissue injury promotes an anti-inflammatory neutrophil phenotype and determines the outcome of inflammation resolution in vivo. *Sci Adv.* 2018;4(9):eaar8320. doi:10.1126/sciadv.aar8320
- Lozada C, del Rio E, Reitberg D, Smith R, Kahn C, Moskowitz RW. A double-blind, randomized, saline-controlled study of the efficacy and safety of co-administered intra-articular injections of Tr14 and Ze14 for treatment of painful osteoarthritis of the knee: The MOZArT trial. *Eur J Integr Med.* 2017:13:54–63.
- Luc B, Gribble PA, Pietrosimone BG. Osteoarthritis prevalence following anterior cruciate ligament reconstruction: a systematic review and numbers-needed-to-treat analysis. *J Athl Train.* 2014;49(6):806–819. doi:10.4085/1062-6050-49.3.35
- Ludwig J, Weiser M. Treating pediatric trauma with a homeopathic ointment. *J Biomed Ther.* 2001;Summer: 8–11.
- Lussignoli S, Bertani S, Metelmann H, Bellavite P, Conforti A. Effect of Traumeel® S, a homeopathic formulation, on blood-induced inflammation in rats. *Complement Ther Med.* 1999;7(4):225–230.
- MacAuley D, Best TM. Reducing risk of injury due to exercise. Stretching before exercise does not help. *BMJ.* 2002; 325(7362):451–452. doi:10.1136/bmj.325.7362.451
- Malemud CJ. Anticytokine therapy for osteoarthritis: evidence to date. *Drugs Aging.* 2010 Feb 1;27(2):95–115. doi:10.2165/11319950-000000000-00000
- Manzoni C, Kia DA, Vandrovcova J, et al. Genome, transcriptome and proteome: the rise of omics data and their integration in biomedical sciences. *Brief Bioinform.* 2018;19(2):286-302. doi:10.1093/bib/bbw114
- Medzhitov R. Inflammation 2010: new adventures of an old flame. *Cell.* 2010;140(6):771–776. doi:10.1016/j.cell.2010.03.006
- Mentlein R, Pufe T. New functions of angiogenic peptides in osteoarthritic cartilage. *Current Rheumatology Reviews.* 2005;1:37–43.
- Muders K, Pilat C, Deuster V, et al. Effects of Traumeel (Tr14) on Exercise-Induced Muscle Damage Response in Healthy Subjects: A Double-Blind RCT. *Mediators Inflamm.* 2016;2016:1693918. doi:10.1155/2016/1693918
- Muders K, Pilat C, Deuster V, et al. Effects of Traumeel (Tr14) on recovery and inflammatory immune response after repeated bouts of exercise: a double-blind RCT. *Eur J Appl Physiol.* 2017;117(3):591–605. doi:10.1007/s00421-017-3554-8
- Müller-Wohlfahrt HW. Mit den Händen sehen. Mein Leben und meine Medizin. Insel Verlag, Berlin 2018.
- Müller-Wohlfahrt H-W. Update: Muscle injuries after 45 years of professional sports care. Georg Thieme Verlag KG, Stuttgart 2021.
- Nathan C, Ding A. Nonresolving inflammation. *Cell.* 2010;140(6):871–882. doi:10.1016/j.cell.2010.02.029

- National Anti Doping Agency of Germany. 2020. Available from: https://www.nada.de/en/medicine/nadamed [Accessed 7 Nov 2022]
- O'Connor JP, Lysz T. Celecoxib, NSAIDs and the skeleton. *Drugs Today.* (Barc.) 2008;44(9):693–709. doi:10.1358/dot.2008.44.9.1251573
- Oo WM, Little C, Duong V, Hunter DJ. The Development of Disease-Modifying Therapies for Osteoarthritis (DMOADs): The Evidence to Date. *Drug Des Devel Ther.* 2021;15:2921–2945. Published 2021 Jul 6. doi:10.2147/DDDT.S295224 fulltext-article-DDDT
- Orchard JW, Best TM, Mueller-Wohlfahrt H-W, et al. The early management of muscle strains in the elite athlete: best practice in a world with a limited evidence basis. *Br J Sports Med.* 2008;42(3):158–159. doi:10.1136/bjsm.2008.04672
- Paoloni JA, Milne C, Orchard J, Hamilton B. Non-steroidal anti-inflammatory drugs in sports medicine: guidelines for practical but sensible use. *Br J Sports Med.* 2009;43(11):863–865. doi:10.1136/bjsm.2009.059980
- Pearle AD, Scanzello CR, George S et al. Elevated high-sensitivity C-reactive protein levels are associated with local inflammatory findings in patients with osteoarthritis. *Osteoarthritis Cartilage.* 2007;15(5):516–523. doi:10.1016/j.joca.2006.10.010
- Porozov S, Cahalon L, Weiser M, Branski D, Lider O, Oberbaum M. Inhibition of IL-1β and TNF-α secretion from resting and activated human immunocytes by the homeopathic medication Traumeel® S. *Clin Dev Immunol.* 2004;11(2):143–149. doi:10.1080/10446670410001722203
- Reinke JM, Sorg H. Wound repair and regeneration. *Eur Surg Res.* 2012;49(1):35–43. doi:10.1159/000339613
- Riordan EA, Little C, Hunter D. Pathogenesis of post-traumatic OA with a view to intervention. *Best Practic Res Clin Rheumatol.* 2014;28:17–30. doi:10.1016/j.berh.2014.02.001
- Rutjes AW, Juni P, da Costa BR, Trelle S, Nuesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. *Ann Intern Med.* 2012;157(3):180–191. doi:10.7326/0003-4819-157-3-201208070-00473
- Sanchez C, Hemmer K, Krömmelbein N, et al. Reduction of Matrix Metallopeptidase 13 and Promotion of Chondrogenesis by Zeel T in Primary Human Osteoarthritic Chondrocytes. *Front Pharmacol.* 2021;12:635034. Published 2021 May 11. doi:10.3389/fphar.2021.635034
- St Laurent G 3rd, Seilheimer B, Tackett M, Zhou J, Shtokalo D, Vyatkin Y et al. Deep Sequencing Transcriptome Analysis of Murine Wound Healing: Effects of a Multicomponent, Multitarget Natural Product Therapy-Tr14. *Front Mol Biosci.* 2017 Aug 17;4:57. doi: 10.3389/ fmolb.2017.00057
- St Laurent G et al. RNAseq Analysis of Treatment-dependent Signaling Changes During Infammation in a Mouse Cutaneous Wound Healing Model. *BMC Genomics.* 2021;22(1):854. Published 2021 Nov 25. doi:10.1186/s12864-021-08083-2
- 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. doi:10.1016/j.explore.2005.08.010
- 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. doi:10.1016/j.ctim.2007.04.004
- Schneider C. Traumeel – an emerging option to nonsteroidal anti-inflammatory drugs in the management of acute musculoskeletal injuries. *Int J Gen Med.* 2011;4:225–234. Published 2011 Mar 25. doi:10.2147/ijGM.S16709
- Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. *Nature.* 2014;510(7503):92–101. doi:10.1038/nature13479

- Serhan CN, Savill J. Resolution of inflammation: the beginning programs the end. *Nat Immunol.* 2005;6(12):1191–1197. doi:10.1038/ni1276
- Serhan CN, Levy BD. Resolvins in inflammation: emergence of the pro-resolving superfamily of mediators. *J Clin Invest.* 2018;128(7):2657–2669. doi:10.1172/JCI97943
- Serhan CN, Gupta SK, Perretti M, et al. The Atlas of Inflammation Resolution (AIR). *Mol Aspects Med.* 2020;74:100894. doi:10.1016/j.mam.2020.100894
- Sorg H, Tilkorn DJ, Hager S, Hauser J, Mirastschijski U. Skin wound healing: An update on the current knowledge and concepts. *Eur Surg Res.* 2017;58(1–2):81-94. doi:10.1159/000454919
- Spector TD, Hart DJ, Byrne J, Harris PA, Dacre JE, Doyle DV. Definition of osteoarthritis of the knee for epidemiological studies. *Ann Rheum Dis.* 1993; 52:790–794. doi:10.1136/ard.52.11.790
- Speed CA. Fortnightly review: Corticosteroid injections in tendon lesions. *BMJ.* 2001;323(7309): 382–386. doi:10.1136/bmj.323.7309.382
- Speed C, Hazleman B, Dalton S. Fast Facts: Soft Tissue Disorders. Second edition. Oxford: Health Press Limited, 2006.
- Strand V, Bloch DA, Leff R, Peloso PM, Simon LS. Safety issues in the development of treatments for osteoarthritis: recommendations of the Safety Considerations Working Group. *Osteoarthritis Cartilage.* 2011:493–499. doi:10.1016/j.joca.2011.02.019
- Sugimoto MA, Sousa LP, Pinho V, Perretti M, Teixeira MM. Resolution of inflammation: what controls its onset? *Front Immunol.* 2016;7:160. doi:10.3389/fimmu.2016.00160
- Sugimoto MA, Vago JP, Perretti M, Teixeira MM. Mediators of the Resolution of the Inflammatory Response. *Trends Immunol.* 2019;40(3):212–227. doi:10.1016/j.it.2019.01.007
- Sullivan WJ, Panagos A, Foye PM, Sable AW, Irwin RW, Zuhosky JP. Industrial medicine and acute musculoskeletal rehabilitation.2. Medications for the treatment of acute musculoskeletal pain. *Arch Phys Med Rehabil.* 2007;88(3 Suppl 1):S10–S13. doi:10.1016/j.apmr.2006.12.009
- Thomopoulos S, Parks WC, Rifkin DB, Derwin KA. Mechanisms of tendon injury and repair. *J Orthop Res.* 2015;33(6):832–839. doi:10.1002/jor.22806
- Thysen S, Luyten FP, Lories RJ. Targets, models and challenges in osteoarthritis research. *Dis Model Mech.* 2015 Jan;8(1):17–30. doi:10.1242/dmm.016881
- Titchenal MR, Chu CR, Erhart-Hledik JC, Andriacchi TP. Early changes in knee center of rotation during walking after anterior cruciate ligament reconstruction correlate with later changes in patient-reported outcomes. *Am J Sports Med.* 2017;45:915–921. doi:10.1177/0363546516673835
- van den Bekerom MP, Struijs PA, Blankevoort L, Welling L, van Dijk CN, Kerkhoffs GM. What is the evidence for rest, ice, compression, and elevation therapy in the treatment of ankle sprains in adults?. *J Athl Train.* 2012;47(4):435–443. doi:10.4085/1062-6050-47.4.14
- Vaudreuil N, Roe J, Salmon L, Servien E, van Eck C. Management of the female anterior cruciate ligament: current concepts *J ISAKOS.* 2020;5:123–127.
- Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. [published correction appears in *Lancet.* 2013 Feb 23;381(9867):628. Al Mazroa, Mohammad A [added]; Memish, Ziad A [added]]. *Lancet.* 2012;380(9859):2163–2196. doi:10.1016/S0140-6736(12)61729-2
- Vuurberg G, Hoorntje A, Wink LM, et al. Diagnosis, treatment and prevention of ankle sprains: update of an evidence-based clinical guideline. *Br J Sports Med.* 2018;52(15):956. doi:10.1136/bjsports-2017-098106. Epub 2018 Mar 7.
- Walsh DA, Pearson CI. Angiogenesis in the pathogenesis of inflammatory joint and lung diseases. *Arthritis Res.* 2001;3(3):147–153. doi:10.1186/ar292

- Wandel S, Juni P, Tendal B, et al. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *BMJ.* 2010; 341 :c4675. Published 2010 Sep 16. doi:10.1136/bmj.c4675
- Waterman BR, Owens BD, Davey S, Zacchilli MA, Belmont PJ Jr. The epidemiology of ankle sprains in the United States. *J Bone Joint Surg Am.* 2010;92(13):2279–2284. doi:10.2106/JBJS.I.01537
- WHO. Musculoskeletal conditions. Available from: https://www.who.int/news-room/fact-sheets/detail/musculoskeletal-conditions [Accessed 16 October 2021]
- Wolfarth B, Speed C, Raymuev K, Vanden Bossche L, Migliore A. Managing pain and inflammation associated with musculoskeletal disease: time for a change? Curr Med Res Opin. 2022;38(10):1695-1701. doi:10.1080/03007995.2022.2108618
- The World Anti-Doping Agency (WADA). 2022 Available from: https://www.wada-ama.org/en/resources/world-anti-doping-program/prohibited-list [Accessed 15 June 2022]
- Zell J, Connert WD, Mau J, Feuerstake G. Behandlung von akuten Sprunggelenksdistorsionen: Doppelblindstudie zum Wirksamkeitsnachweis eines homoopathischen Salbenpraparats. *Fortschr Med.* 1988;106(5):96–100. English translation available in *Biol Ther.* 1989;VII(1):1–6.
- 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):301–10.
- Zenner S, Metelmann H. Therapy experience with a homeopathic ointment: results of drug surveillance conducted on 3,422 patients. *Biol Ther.* 1994;XII(3):204–11.
- Zenner S, Weiser M. Oral treatment of traumatic, inflammatory, and degenerative conditions with a homeopathic remedy. *Biomed Ther.* 1997;XV:22–6.

12 SUMMARY OF PRODUCT CHARACTERISTICS

This is the master version of the Traumeel® Summary of Product Characteristics (SmPC).
For local adaptation and approval, please refer to your local Traumeel® SmPC.

TRAUMEEL® FORMULATIONS AND DOSING RECOMMENDATIONS

Traumeel®: Tablets • Solution for Injection • Ointment • Gel • Drops

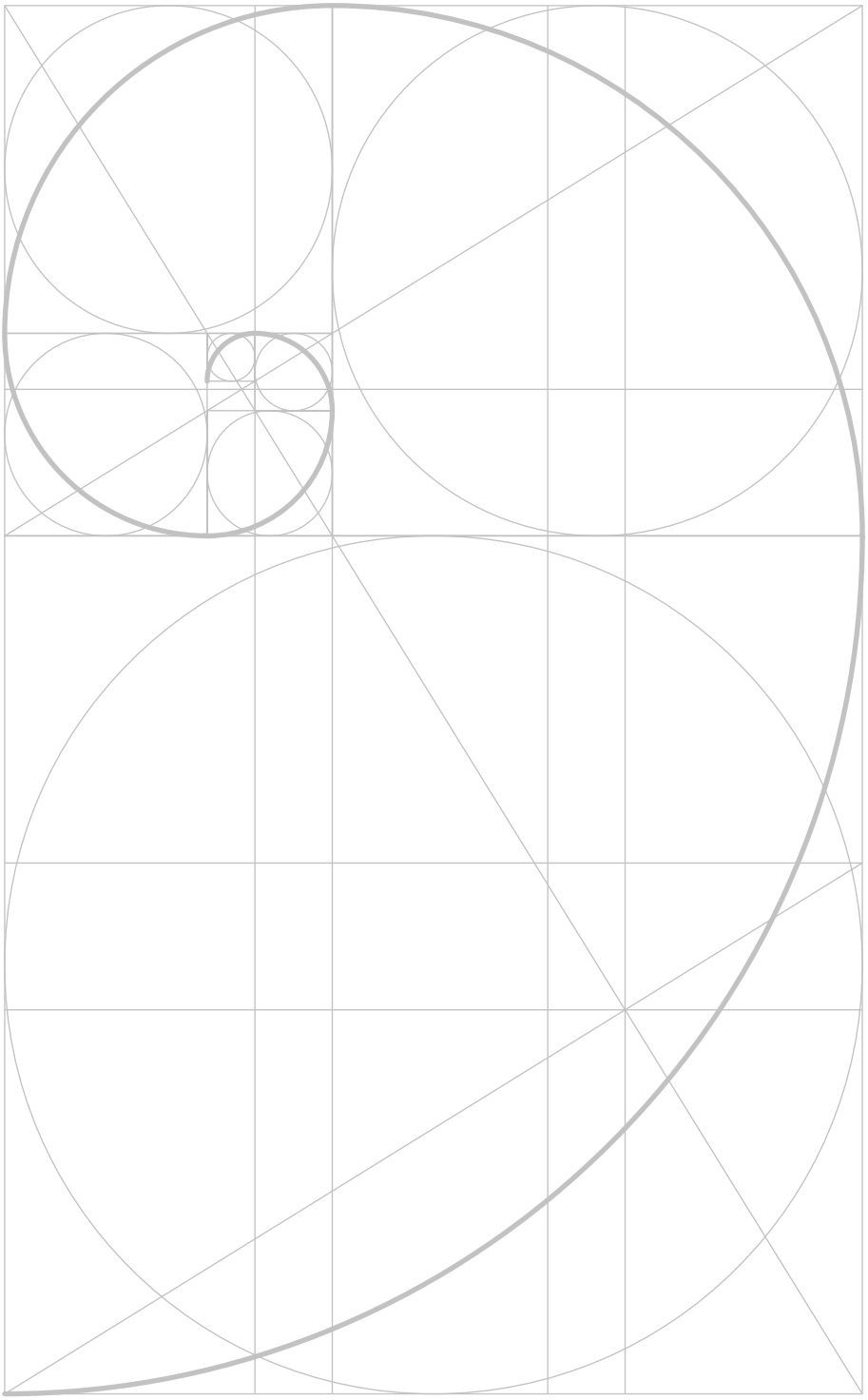
Compositions: Tablets: 1 tablet containing: Active ingredients: Achillea millefolium D3 15.0 mg; Aconitum napellus D3 30.0 mg; Atropa belladonna D4 75.0 mg; Hepar sulfuris D8 30.0 mg; Matricaria recutita D3 24.0 mg; Mercurius solubilis Hahnemanni D8 30.0 mg; Symphytum officinale D8 24.0 mg; Bellis perennis D2 6.0 mg; Calendula officinalis D2 15.0 mg; Echinacea D2 6.0 mg; Echinacea purpurea D2 6.0 mg; Hamamelis virginiana D2 15.0 mg; Hypericum perforatum D2 3.0 mg; Arnica montana D2 15.0 mg. Excipients: Lactose monohydrate 6.0 mg; Magnesium stearate 1.5 mg. **Contains lactose! Please see package insert! Solution for Injection:** 1 ampoule of 2.2 ml (= 2.2 g) contains: Active ingredients: Achillea millefolium D3 2.20 mg; Matricaria recutita D3 2.20 mg; Symphytum officinale D6 2.20 mg; Aconitum napellus D2 1.32 mg; Atropa belladonna D2 2.20 mg; Bellis perennis D2 1.10 mg; Calendula officinalis D2 2.20 mg; Echinacea D2 0.55 mg; Echinacea purpurea D2 0.55 mg; Hypericum perforatum D2 0.66 mg; Hepar sulfuris D6 2.20 mg; Mercurius solubilis Hahnemanni D6 1.10 mg; Hamamelis virginiana D1 0.22 mg; Arnica montana D2 2.20 mg. Excipients: Sodium chloride 19.4 mg, Water for injections 2179.1 mg. **Ointment:** 100 g containing: Active ingredients: Achillea millefolium D4 0.090 g; Aconitum napellus D4 0.050 g; Arnica montana D4 1.500 g; Atropa belladonna D4 0.050 g; Bellis perennis D4 0.100 g; Calendula officinalis D4 0.450 g; Echinacea D4 0.150 g; Echinacea purpurea D4 0.150 g; Hamamelis virginiana D4 0.450 g; Hepar sulfuris D6 0.025 g; Hypericum perforatum D6 0.090 g; Matricaria recutita D4 0.150 g; Mercurius solubilis Hahnemanni D6 0.040 g; Symphytum officinale D4 0.100 g. Excipients: Paraffin, liquid 9.342 g; Cetostearyl alcohol (type A), emulsifying 8.007 g; Paraffin, white soft 9.342 g; Water, purified 60.579 g; Ethanol (96%) 9.335 g; Preserved with 12.7 vol.-% alcohol. **Gel:** 100 g containing: Active ingredients: Achillea millefolium D0 0.090 g; Aconitum napellus D1 0.050 g; Arnica montana D3 1.500 g; Atropa belladonna D1 0.050 g; Bellis perennis D0 0.100 g; Calendula officinalis D0 0.450 g; Echinacea D0 0.150 g; Echinacea purpurea D0 0.150 g; Hamamelis virginiana D0 0.450 g; Hepar sulfuris D6 0.025 g; Hypericum perforatum D6 0.090 g; Matricaria recutita D0 0.150 g; Mercurius solubilis Hahnemanni D6 0.040 g; Symphytum officinale D4 0.100 g. Excipients: Water, purified 74.652 g; Ethanol (96%) 18.653 g; Carbomers (Carbopol 980NF) 1.000 g; Sodium hydroxide solution 18% (m/m) 2.300 g; Contains 24.4 vol.-% alcohol. Purified water, ethanol 96% (V/V), carbomers, sodium hydroxide solution 18% m/m. **Drops:** 100 g containing: Active ingredients: Aconitum napellus D3 10.0 g; Atropa belladonna D4 25.0 g; Symphytum officinale D8 8.0 g; Achillea millefolium D3 5.0 g; Calendula officinalis D2 5.0 g; Echinacea D2 2.0 g; Echinacea purpurea D2 2.0 g; Hamamelis virginiana D2 5.0 g; Hypericum perforatum D2 1.0 g; Matricaria recutita D3 8.0 g; Hepar sulfuris D8 10.0 g; Mercurius solubilis Hahnemanni D8 10.0 g; Arnica montana D2 5.0 g; Bellis perennis D2 2.0 g. Excipients: Water, purified 2.0 g; Contains 35 vol.-% alcohol.
Indications: Tablets, Solution for Injection, Ointment, Gel, Drops: The medicinal product is used for the treatment of various inflammatory conditions including injuries, especially of the musculoskeletal system.
Contraindications: Tablets, Solution for Injection, Gel, Drops: 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). **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. As this product contains Echinacea, individual evaluation is recommended before prescribing this product in patients with immune system dysfunction, e.g. cases of progressive systemic disorders, autoimmune diseases, immunodeficiencies, immunosuppression and diseases of the white blood cell system. **Solution for Injection:** As this product contains Echinacea, individual evaluation is recommended before prescribing this product in patients with immune system dysfunction, e.g. cases of progressive systemic disorders, autoimmune diseases, immunodeficiencies, immunosuppression and diseases of the white blood cell system. **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. **Drops:** This medicinal product contains 35 vol.-% ethanol (alcohol). As this product contains Echinacea, individual evaluation is recommended before prescribing this product in patients with immune system dysfunction, e.g. cases of progressive systemic disorders, autoimmune diseases, immunodeficiencies, immunosuppression and diseases of the white blood cell system.
Side effects: Like all medicinal products, this homeopathic medicinal product can cause side effects, although not everybody gets them. **Tablets:** In isolated cases transient skin reactions have been reported. **Solution for Injection:** In isolated cases transient allergic (hypersensitivity) reactions (e.g. skin allergies, redness/swelling at the injection site, even up to anaphylaxis) have been reported. **Ointment:** In isolated cases transient skin reactions have been reported. **Gel:** In isolated cases transient skin reactions (eg. rash, itchiness) have been reported. **Drops:** In isolated cases transient allergic skin reactions have been reported.
Interactions with other medication: Tablets: None have been reported, and none are expected due to the homeopathic dilutions. **Solution for Injection, Drops:** No interactions have been reported, and none are expected due to the homeopathic dilutions. **Ointment, Gel:** No interactions have been reported, and none are expected due to the homeopathic dilutions and external use.
Pregnancy and lactation: For this product no clinical data on pregnancy and lactation are available. Homeopathic dilutions of the substances present in this medicinal product are not known to be harmful during pregnancy and lactation. No adverse effects have so far been reported.

Effects on ability to drive and use machines: **Tablets, Solution for Injection:** 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. **Drops:** This medicinal product has no or negligible influence on the ability to drive and use machines.
Dosage: **Tablets:** Unless otherwise prescribed: Standard dosage: *Adults (and children 12 yrs. and older):* 1 tablet 3× daily. *Pediatric:* below 2 yrs.: 1 tablet 1× daily. 2–5 yrs.: 1 tablet 1–2× daily. 6–11 yrs.: 1 tablet 2× daily. Acute or initial dosage: *Adults (and children 12 yrs. and older):* 1 tablet every ½ to1 hr., up to 12× daily, and then continue with standard dosage. *Pediatric:* below 2 yrs.: 1 tablet every 1 to 2 hrs., up to 4× 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. 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. **Solution for Injection:** unless otherwise prescribed: Standard dosage: *Adults (and children 12 yrs. and older):* 1 ampoule 1 to 3× weekly. *Pediatric:* 2–5 yrs.: ½ ampoule 1 to 3x 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. *Pediatric:* 2–5 yrs.: ½ 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.a., i.d., i.m. or i.v. route. **Ointment, Gel:** Unless otherwise prescribed: Standard dosage: *Adults (and children 12 yrs. and older):* apply 2× daily, or more often if needed. *Paediatric:* below 2 yrs.: apply 2× daily, or more often if needed. 2–5 yrs.: apply 2× daily, or more often if needed. 6–11 yrs.: 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. **Drops:** unless otherwise prescribed: Standard dosage: *Adults (and children 12 yrs. and older):* 10 drops 3× daily. *Pediatric:* below 2 yrs.: 3 drops 3× daily. 2–5 yrs.: 5 drops 3× daily. 6–11 yrs.: 7 drops 3× daily. Acute or initial dosage: *Adults (and children 12 yrs. and older):* 10 drops every ½ to 1 hr., up to 12× daily, and then continue with standard dosage. *Pediatric:* below 2 yrs.: 3 drops every ½ to 1 hr., up to 12× daily, and then continue with standard dosage. 2–5 yrs.: 5 drops every ½ to 1 hr., up to 12× daily, and then continue with standard dosage. 6–11 yrs.: 7 drops every ½ to 1 hr., up to 12× daily, and then continue with standard dosage. Method of administration: This medicine should be taken away from meals. For children, add drops to a small amount of water.
Duration of use: **Tablets, Solution for Injection, Drops:** As this product contains Echinacea, individual evaluation is recommended before prescribing this product for periods longer than 8 weeks.
Overdose: **Tablets, Solution for Injection, Drops:** 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. (9753) **Solution for Injection:** Packs containing 5, 10, 50 and 100 ampoules of 2.2 ml. (8561) **Ointment:** Tubes containing 50 and 100 g of ointment. (9932). **Gel:** Tubes containing 50 and 100 g of gel. (9934) **Drops:** Drop bottles containing 30 and 100 ml. (9804).

Version 2016

13 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.



Biologische Heilmittel Heel GmbH
Dr. Reckeweg-Straße 2-4,
76532 Baden-Baden
Germany

Tel. +49 (0) 7221 5 01 00
info@heel.com
www.traumeel.com
www.inflammres.com
www.heel.com

-Heel
Healthcare designed by nature