

# Review of the Clinical Efficacy of the Multicomponent Combination Medication Traumeel and Its Components

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**Objective** • Musculoskeletal injuries and inflammation are the most common indications for use of the multicomponent combination medication, Traumeel. This article reviews the clinical evidence for the safety and efficacy of Traumeel and discusses its use as an alternative to nonsteroidal antiinflammatory drugs (NSAIDs).

**Methods** • A systematic database search for pharmacological and clinical studies and case reports of Traumeel and its constituents in registered and unregistered indications was conducted. The immunomodulatory mode of action, safety, and efficacy of Traumeel was reviewed.

**Results** • Six randomized, controlled studies; 19 nonrandomized, controlled studies; four cohort studies; and numerous case reports investigating the different application forms of Traumeel (injection solution, tablets, drops, ointment, gel) were identified. Various preclinical and clinical investigations with the constituents were also found. Unlike conventional NSAIDs, Traumeel does not directly inhibit prostaglandin synthesis. It has antioxidative and immunomodulatory properties and appears to modulate arachidonic acid by decreasing the

activity of phospholipase A2. Traumeel is reported to provide effective pain relief and reduce inflammation in patients with acute and subacute musculoskeletal disorders, physical trauma, and sport injuries. Successful treatment of hemarthrosis-related effusions and a reduction of joint pain associated with fibromyalgia was also demonstrated. Traumeel ointment reduced swelling and improved joint mobility in patients with sport-related ankle sprain. There is also evidence that Traumeel is of comparable efficacy to NSAIDs in the treatment of epicondylitis and tendinosis. Data from clinical studies and reports during more than 60 years of use in clinical practice support the excellent safety profile of Traumeel. The risk of hypersensitivity or allergic reactions is very low.

**Conclusions** • Rapid pain relief and antiinflammatory effects were observed in patients with acute or subacute musculoskeletal problems treated with Traumeel. Traumeel may be considered an effective and well-tolerated alternative to NSAIDs for the first-line treatment of physical trauma and sport injuries. (*Altern Ther Health Med*. 2011;17(2 Suppl):S18-S31.)

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The multicomponent combination medication, Traumeel (Biologische Heilmittel Heel GmbH, Germany) is widely used for physical trauma, sport injuries, and degenerative and immunological disorders. It contains 12 botanical and two mineral substances in micro- or ultra low-dilutions. Traumeel has pronounced analgesic, antiedematous, and antiexudative effects, and treatment results in rapid reduction of inflammation, pain relief, recovery from bruising, and healing promotion.

The clinical use of Traumeel is based on the bioregulatory understanding of the origin of diseases and their cures. The bioregulatory concept defines illnesses as defense mechanisms against harmful exogenous and endogenous substances. Such harmful substances, originally called homotoxins by Hans Heinrich

Reckeweg, impair the balance between the extracellular matrix (ECM) and cellular metabolism. In bioregulatory medicine, achieving a bioregulatory balance between pro- and antiinflammatory cytokines is considered to be the critical step in recovery.

Reckeweg's bioregulatory concept has many aspects in common with the modern understanding of immunology, such as psycho-neuro-endocrine-immunological complexity. It includes modern hypotheses for the mode of action of micro- or ultra low-dose solutions such as the immunological bystander reaction,<sup>1</sup> and integrates the reticuloendothelial and the adenohypophyseal systems, neural reflexes, connective tissue detoxification functions, and liver detoxification.<sup>2</sup>

The dynamic view of disease states and defense mechanisms against harmful substances allows prediction of possible further developments of the pathological condition (progression or regression). Reckeweg defined six phases of action, with phases 1, 2, and 3 being humoral (the excretion, inflammation, and deposition phases, respectively) and phases 4, 5, and 6 being cellular (the impregnation, degeneration, and neoplasm phases, respectively). Changes in pathological condition are called vicariation, which includes improvement (regressive vicariation) and

worsening (progressive vicariation). The objective of bioregulatory treatment, such as with Traumeel, is regressive vicariation.

Alfred Pischinger developed a theory based on the regulation of the ECM (“ground regulation”). He defined this system as a functional unit comprising the final vascular pathway, the connective tissue cells, and the final vegetative-nervous structure containing cellular elements like fibrocytes and immune cells. Among these cells and structures, the extracellular fluid and associated lymph system create the “milieu interior” (or ECM), which is the area of basic vital functions and body self-regulation. Pischinger postulated that all organs and cellular components are dependent on the dynamic flow in the ECM, which responds to stimuli and is the origin of many immunological and pathological actions (eg, inflammation).<sup>3</sup>

According to Reckeweg, acute inflammation is an action by the ECM to remove disease-producing harmful substances. In his theory, chronic inflammation can be understood as “disease provoking” due to suppression of inflammation, recurrent infection, intoxication, or autoimmunity. Medications with bioregulatory properties, such as Traumeel, might engage the inflammatory response to repair physiological damage within the patient without affecting the self-regulating control of the inflammatory process. These medications are not only symptom-specific, but also patient-specific. As addressed in the article by Cesnulevicius in this supplement, which discusses possible biological activities of Traumeel within the pathophysiological model of overuse musculoskeletal disorders, these medications don’t simply suppress the symptoms, but support metabolism and immune responses in the framework of a given autoregulatory system.

This article reviews the evidence supporting the clinical use of Traumeel. Particular focus is on the contribution of immunomodulatory and antiinflammatory effects to Traumeel’s broad clinical efficacy. Additionally, the clinical use of Traumeel as an equally effective but better tolerated alternative to nonsteroidal antiinflammatory drugs (NSAIDs) is presented. A bioregulatory treatment approach might be considered particularly beneficial to patients with poor tolerance to NSAIDs. Unlike conventional NSAIDs, Traumeel does not inhibit the arachidonic pathway of prostaglandin and comparisons are made between the different modes of action.

## METHODS

### Formulations

Five different galenic application forms of Traumeel are currently marketed, including injection solution, tablets, drops, ointment, and gel. The composition of each formulation is presented in Tables 1 through 3.

### Registered Indications

**Systemic Application Forms.** The systemic application forms of Traumeel are injection solution, tablets, and drops. Registered indications for these forms of administration include blunt injuries (eg, sprains, dislocations, contusions, hemarthrosis, and effusions into a joint); fractures; postoperative and posttraumatic edema and swelling of the soft tissues; inflammatory and

**TABLE 1** Composition of Traumeel Injection Solution

Component	Dilution	Injection Solution* (2.2 mL)
<i>Arnica montana</i>	D2	2.2 µL
<i>Calendula officinalis</i>	D2	2.2 µL
<i>Hamamelis virginiana</i>	D1	0.22 µL
<i>Achillea millefolium</i>	D3	2.2 µL
<i>Atropa belladonna</i>	D2	2.2 µL
<i>Aconitum napellus</i>	D2	1.32 µL
<i>Mercurius solubilis Hahnemannii</i>	D6	1.1 µL
<i>Hepar sulfuris</i>	D6	2.2 µL
<i>Chamomilla recutita</i>	D3	2.2 µL
<i>Symphytum officinale</i>	D6	2.2 µL
<i>Bellis perennis</i>	D2	1.1 µL
<i>Echinacea angustifolia</i>	D2	0.55 µL
<i>Echinacea purpurea</i>	D2	0.55 µL
<i>Hypericum perforatum</i>	D2	0.66 µL

\*Contains water for injection and sodium chloride.

**TABLE 2** Composition of Oral Preparations of Traumeel

	Dilution	1 tablet*	Drops† (100 g)
<i>Arnica montana</i>	D2	15 mg	5 g
<i>Calendula officinalis</i>	D2	15 mg	5 g
<i>Hamamelis virginiana</i>	D2	15 mg	5 g
<i>Achillea millefolium</i>	D3	15 mg	5 g
<i>Atropa belladonna</i>	D4	75 mg	25 g
<i>Aconitum napellus</i>	D3	30 mg	10 g
<i>Mercurius solubilis Hahnemannii</i>	D8	30 mg	10 g
<i>Hepar sulfuris</i>	D8	30 mg	10 g
<i>Chamomilla recutita</i>	D3	24 mg	8 g
<i>Symphytum officinale</i>	D8	24 mg	8 g
<i>Bellis perennis</i>	D2	6 mg	2 g
<i>Echinacea angustifolia</i>	D2	6 mg	2 g
<i>Echinacea purpurea</i>	D2	6 mg	2 g
<i>Hypericum perforatum</i>	D2	3 mg	1 g

\*Contains lactulose monohydrate; †Contains 35 vol-% alcohol.

degenerative processes associated with inflammation, arthrosis of the hip, knee, and small joints; and acute cerebral contusions.

**Topical Application Forms.** Topical application forms include an ointment and gel. Traumeel ointment and gel are indicated for blunt injuries (eg, sprains, dislocations, contusions, hemarthrosis, and effusions into a joint), closed fractures, inflammatory and

**TABLE 3** Composition of Topical Traumeel Preparations

	Dilution	Ointment* (100 g)	Gel† (100 g)
<i>Arnica montana</i>	D3	1.5 g	1.5 g
<i>Calendula officinalis</i>	Æ	0.45 g	0.15 g
<i>Hamamelis virginiana</i>	Æ	0.45 g	0.15 g
<i>Echinacea angustifolia</i>	Æ	0.15 g	0.15 g
<i>Echinacea purpurea</i>	Æ	0.15 g	0.15 g
<i>Chamomilla recutita</i>	Æ	0.15 g	0.15 g
<i>Symphytum officinale</i>	D4	0.1 g	0.1 g
<i>Bellis perennis</i>	Æ	0.1 g	0.1 g
<i>Hypericum perforatum</i>	D6	0.09 g	0.09 g
<i>Achillea millefolium</i>	Æ	0.09 g	0.09 g
<i>Aconitum napellus</i>	D1	0.05 g	0.05 g
<i>Atropa belladonna</i>	D1	0.05 g	0.05 g
<i>Mercurius solubilis</i>	D6	0.04 g	0.04 g
<i>Hahnemannia</i>			
<i>Hepar sulfuris</i>	D6	0.025 g	0.025 g

\*Based on hydrophilic ointment (DAB), preserved with 12.5 volume-% alcohol;

†contains 25% alcohol; D, dilution; Æ, *Tinctura Mater* (Mother Tincture).

degenerative processes (particularly of the tissues providing support and mobility), and arthrosis of the hip, knee, and small joints.

### Search Strategy

A comprehensive literature search of AMED, Medline, Embase, and the Cochrane library to identify all studies on Traumeel and its constituents was performed. All common and scientific names of Traumeel and its constituents were used to identify the studies. All Traumeel literature published between 1966 and March 2007 reporting efficacy in humans, dosing, precautions, adverse events (clinical and laboratory parameters), use in pregnancy/lactation, and mode of action were included in the review. The search for published articles investigating the constituents of Traumeel focused on the period from January 2000 to March 2007, although the reference lists of earlier studies were also scanned for important studies for inclusion.

### Evaluation

All clinical studies on Traumeel and/or its constituents were reviewed, listed, and reported. Studies investigating Traumeel and those reporting on its constituents were reviewed separately. The quality of the randomized, controlled trials was assessed using the Jadad score,<sup>4</sup> a validated instrument for measuring the methodological quality on a scale of 0 (poor) to 5 (good).

### Analysis

Clinical efficacy and safety data on Traumeel, its constituents, and placebo and active controls were reviewed in the context of findings from modern immunological research. Several

mechanisms probably contributing to the clinical efficacy of Traumeel in several indications were discussed, along with the possible effects of the constituents on immunological processes.

## RESULTS

### Overview of Studies and Investigations

**Preclinical Investigations.** In preclinical investigations, Traumeel showed a broad range of antiinflammatory and immunomodulatory effects in vitro and in vivo. Wound healing and antioxidative effects were also demonstrated in animal models.

**Clinical Efficacy.** The Traumeel clinical trial program included six randomized, controlled studies; 19 nonrandomized, controlled studies; and four cohort studies (Table 4). There are also numerous case reports detailing the use of Traumeel. All five galenic forms of Traumeel (injection solution, tablets, drops, ointment, and gel) were studied in a broad range of registered and unregistered indications.

### Efficacy in Registered Indications

**Acute Sport Injuries.** In a randomized, double-blind study investigating treatment effects on joint mobility (primary efficacy variable), pain on motion, and angulations of supination (affected joint vs nonaffected contralateral joint), Traumeel ointment (n = 36) was compared to placebo (ointment base; n = 37) in patients with ankle sprains.<sup>5</sup> All patients also received electrotherapy as a basic treatment. Traumeel ointment significantly improved joint mobility at day 10 ( $P < .05$ ) and pain on motion ( $P < .0001$ ). The study was considered to be well conducted and reported (Jadad score = 4), although the randomization procedure was not described.

In another randomized, double-blind study, 102 patients with acute sport injuries (sprains, contusions grade 1-2) were treated with Traumeel S ointment (n = 34), Traumeel-Sine (contains five compounds only; n = 34), or placebo (ointment base; n = 34).<sup>6</sup> Treatment (2 x 10 g ointment daily) was started at latest on day 4 after the injury. Swelling (primary objective) was substantially reduced by Traumeel at day 15, but the reduction vs placebo was statistically significant for the Traumeel Sine group only. Increase in maximum muscle force, reduction of pain, and time to resumption of training were superior for patients in the Traumeel group. The methodological quality of this study was good (Jadad score = 4) and included descriptions of randomization, statistical evaluation, inclusion/exclusion criteria, and continuous quality assurance during the trial.

In a comparison between Traumeel S ointment (n = 25) and Traumeel S ointment plus galvanic electricity (n = 25) in competitive athletes with lateral ligament overextension of the malleolar (supination-distorsion trauma), pain at rest was reduced in both treatment groups up to day 7.<sup>7</sup> However, Traumeel monotherapy had a more pronounced effect on pain from pressure and pain on motion.

Traumeel S drops (3 x 10 drops/day) were compared with conventional standard therapy in 75 patients with soft tissue contusions and fractures in a nonrandomized study. Treatment success was observed in most patients within 5 days.<sup>8</sup> There was

evidence of a dose-related effect; 3 x 30 drops/day appeared to be more effective than 3 x 10 drops/day. A dose-related effect was also observed in a comparison between Traumeel S drops 3 x 15 drops/day and 3 x 10 drops/day as add-on treatment to Traumeel ointment.<sup>9</sup> After removal of the plaster cast, the higher dose seemed to reduce the circumference of the affected extremity more effectively than the lower dose in 26 patients with soft tissue swelling due to bone fractures.

Further evidence of the efficacy of Traumeel ointment was observed in a multicenter drug monitoring trial, which included 3422 patients with different musculoskeletal injuries.<sup>10</sup> The efficacy of Traumeel was assessed as “very good” or “good” in 48.3% and 38.4% of patients, respectively.

**Hemarthrosis.** A randomized, double-blind study comparing Traumeel injection solution (2 mL intra-articular injections on days 1, 4, and 8) with placebo (2 mL intra-articular injections of sodium chloride solution on days 1, 4, and 8) in 73 patients with injury-related hemarthrosis of the knee demonstrated that Traumeel was superior to placebo in assessments of joint circumference and mobility, pain intensity, and effusion volume.<sup>11</sup> However, the methodological and reporting of this study was poor (Jadad score=1).

In patients with acute traumatic effusions of the knee joint (hemarthrosis and hydrarthrosis), Traumeel injection (2.2 mL intra-articular injection) after hematoma aspiration reduced the rate of recurrence after 3 weeks compared to standard basic treatment.<sup>12</sup> A total of 89% (25/28) of patients treated with Traumeel were without detectable effusions compared with 21% (4/19) patients in the control group.

**Epicondylitis.** In an open-label, nonrandomized, multicenter study, treatment with local injections (2.2 mL) of Traumeel S were compared with intramuscular injections of NSAIDs (mainly diclofenac) in 184 patients with epicondylitis.<sup>13</sup> Additional treatments and physiotherapy were permitted during the observation period of 2 weeks, but patients receiving Traumeel could not receive NSAIDs and patients receiving an NSAID could not receive micro- or ultra low-diluted remedies. The study provided evidence for the noninferiority of Traumeel with regard to NSAIDs. Significantly greater improvement in pain at rest and mobility (change in torsional and extensional joint mobility) was reported following treatment with Traumeel compared with NSAIDs.

**Tendinosis.** Patients with tendinosis were studied in an open-label, nonrandomized, controlled study comparing thermotherapy (Hydrosun; n = 84), Traumeel injections (2 x 1 ampoule [2 mL] injection solution per week; n = 48), and the combination of thermotherapy plus Traumeel injections (2 x 1 ampoule [2 mL] injection solution per week; n = 79).<sup>14</sup> Traumeel was mixed with mecaine 1% and injected into the tender points; treatment was administered for 4 to 6 weeks. Traumeel injections alone were found to be the most effective treatment, followed by combination therapy. Pre- and posttreatment assessments using a visual analogue scale (VAS) showed that pain levels in patients receiving Traumeel monotherapy improved significantly after 3

to 4 weeks ( $P < .001$ ) and was maintained for at least 12 months after treatment discontinuation.

An observational study in 357 patients with acute and chronic tendinopathies also demonstrated that the efficacy of 28 days of local treatment with Traumeel ointment was comparable to that of diclofenac gel.<sup>15</sup> Improvements were observed in most patients after 3 to 7 days of treatment. Pain scores decreased by  $5.7 \pm 2$  and  $5.0 \pm 2.7$  in the Traumeel and diclofenac groups, respectively, and mobility scores also showed comparable improvements.

**Fibromyalgia.** In a single-center, double-blind study, a bioregulatory combination therapy comprising Traumeel, Spascuprel, Graphites Homacord, Cerebrum compositum, and Thalamus compositum was compared with placebo (saline) in 20 patients with clinically diagnosed fibromyalgia.<sup>16</sup> The bioregulatory combination therapy was administered by twice-weekly mesoinjections over the trigger points sensitive to digital pressure. After 8 weeks, muscular pain at the painful points was significantly reduced, and psychological status was improved in patients receiving the bioregulatory combination therapy compared with placebo. Methods achieving the double-blind conditions were not described, and therefore the Jadad score was rated low (=1).

**Rheumatoid Arthritis.** The effect of Traumeel S drops on the number of regulatory T-cells (% of  $10^6$  T helper-cells) in patients with mild rheumatoid arthritis was investigated in an open-label, nonrandomized study.<sup>17</sup> The number of regulatory T-cells increased in seven patients (five patients showed a moderate increase, and two showed a large increase) and decreased in two patients. The findings of this pilot study in patients with rheumatoid arthritis suggest Traumeel has an immunomodulatory effect, which needs to be confirmed in a more rigorous randomized, controlled, clinical trial.

**Degenerative and Traumatic Musculoskeletal Complaints.** A large observational study reported the outcomes of 3241 patients with degenerative and traumatic musculoskeletal complaints, including arthrosis, myogenesis, sprains/distortions, periarthropathia humeroscapularis, epicondylitis, and tendovaginitis, following treatment with Traumeel injections.<sup>18</sup> All patients received Traumeel injections during routine clinical practice for periods ranging from less than 1 week to more than 6 months. Physicians rated the efficacy of Traumeel as “good” or “very good” in 78.8% of patients and reported that only 3.5% of cases showed no improvement.

Another large observational study in 1359 outpatients also reported the efficacy of Traumeel S tablets and drops to be “good” or “very good” in the treatment of injuries and inflammatory conditions in 80% of patients.<sup>19</sup>

#### Efficacy in Nonregistered Indications

**Chemotherapy-induced Mucositis.** Traumeel demonstrated significant benefits to patients with stomatitis undergoing allogenic (n = 16) or autologous (n = 16) stem cell transplantation, as assessed by the World Health Organization (WHO) stomatitis score.<sup>20</sup> In this study, patients were randomized to 5 x 1 ampoule/day of Traumeel injection administered as a mouth rinse (n = 17) or

TABLE 4 Overview of Randomized and Nonrandomized Clinical Studies of Different Applications of Traumeel

Study Reference	n	Indication	Control Group
Randomized studies			
Boehmer et al 1992 <sup>6</sup>	102	Acute sport injuries	Placebo (ointment base)
Zell et al 1988 <sup>5</sup>	73	Ankle sprains (sports-related)	Placebo (ointment base)
Thiel et al 1991 <sup>11</sup>	73	Hemarthrosis	Placebo
Ecocheaga et al 2004 <sup>16</sup>	20	Fibromyalgia	Placebo
Oberbaum et al 2001 <sup>20</sup>	32	Chemotherapy-induced mucositis	Placebo
Matusiewicz et al 1996 <sup>22</sup>	103	Corticosteroid-dependent asthma bronchiale	Placebo
Nonrandomized studies			
Kunt 1983 <sup>12</sup>	37	Hemarthrosis and/or hydrarthrosis of a joint	Placebo
Präg 2004 <sup>14</sup>	211	Tendinosis	Thermotherapy (Hydrosun), thermotherapy plus Traumeel
Timmermann et al 1998 <sup>52</sup>	236	Lumbar syndrome	Hydrocortisone; hydrocortisone plus Traumeel
Birnesser et al 2004 <sup>13</sup>	184	Epicondylitis	NSAIDs (mainly diclofenac)
Heine et al 2002 <sup>17</sup>	10	Rheumatoid arthritis	No control group
Geiger 1968 <sup>8</sup>	75	Posttraumatic soft tissue contusions and fractures	Conventional treatment
Mergen 1983 <sup>9</sup>	26	Posttraumatic soft tissue contusions and fractures	Traumeel ointment plus two doses of Traumeel drops
Thiel 1987 <sup>53</sup>	50	Supination-distortion trauma	Galvanic electricity
Oberbaum et al 1998 <sup>21</sup>	27	Chemotherapy-induced mucositis	No special treatment
Konca et al 1997 <sup>4</sup>	80	Tonsillectomy, postoperative course	Standard treatment
Matusiewicz et al 1997 <sup>23</sup>	50	Corticosteroid-dependent asthma bronchiale	Placebo
Singer et al 2007 <sup>54</sup>	30	Postoperative pain	No special treatment
Grudyanov et al 2006 <sup>55</sup>	141	Inflammatory peridontal disease	Conventional therapy
Grudyanov et al 2007 <sup>56</sup>	112	Inflammatory peridontal disease	Different Traumeel treatments
Ribot-Florit 2001 <sup>57</sup>	66	Dental extraction (symptom control)	Analgesics, NSAIDs
Ostazewska et al 1997 <sup>58</sup>	40	Postoperative complaints	Ointment monotherapy; ointment plus laser biostimulation; ointment plus laser biostimulation plus phonophoresis
Larentsova et al 2002 <sup>59</sup>	105	Peridontitis	Conventional treatment
Zilinskas 2002 <sup>60</sup>	42	Gingivitis, peridontitis	Laser scalar plus chlorhexidine
Diaz et al 1998 <sup>61</sup>	78	Dental root canal treatment	Standard treatment

\*Only 5 compounds; NSAIDs indicates nonsteroidal antiinflammatory drugs.

TABLE 4, continued

Galenic Form	Jadad Score	Outcome
Ointment (Traumeel Sine)*	4	Significant reduction of circumference with Traumeel Sine vs placebo ( $P=.028$ )
Ointment	4	Day-time joint mobility significantly improved ( $P=.005$ ) Pain on motion significantly improved at day 10 ( $P<.0001$ )
Injection solution	1	Superior joint mobility and pain relief, and lower effusion volume in Traumeel group
Injection solution	1	Pre- and posttreatment comparison showed improvements in muscular pain and pain in painful joints
Ampoules as a mouth rinse	4	Significantly reduced stomatitis score ( $P<.01$ ) and fewer case of stomatitis and worsening
Injection solution	3	Pre- and posttreatment comparisons showed improvement of spirometric parameters, granulocyte migration, IgE, and steroid demand in the verum group
Injection solution	—	No detectable recurrence of effusions in the Traumeel group compared to recurrences in most control patients
Injection solution	—	Traumeel was more effective than Hydrosun
Injection solution	—	Traumeel monotherapy and in combination with hydrocortisone can be effective
Injection solution	—	Proof of noninferiority of Traumeel compared to NSAIDs
Drops	—	Immunomodulating effect on regulatory T-cells lymphocytes
Drops	—	Most patients were successfully treated within 5 days. Traumeel 3 x 30 drops/d were more effective than 3 x 10 drops/d
Drops and ointment	—	Higher dose of Traumeel (3 x 15 drops/d) more effective than lower dose (3 x 10 drops/d)
Ointment	—	Traumeel ointment more effective than galvanic electricity
Injection solutions as a mouth rinse	—	Traumeel reduced the duration of mucositis symptoms
Injection solution	—	Traumeel improved postoperative recovery (earlier mouth opening and acceptance of food) vs standard care
Injection solution plus Engystol	—	Remarkable reduction of steroid demand with Traumeel
Injection solution only; injection solution followed by oral treatment	—	Lower consumption of analgesics in patients treated with Traumeel (injection with or without oral treatment)
Tablets; injections solution; Engystol	—	Slightly positive effect of Traumeel compared to conventional therapy Engystol® had a more rapid effect than Traumeel
Tablets; injection solution; ointment; injection solution as mouth wash	—	Comparable efficacy of the different Traumeel application forms
Tablets	—	Reduction of pain, inflammation, and hemorrhage with Traumeel
Ointment	—	Traumeel ointment was useful in the treatment of postoperative complications
Ointment; ointment plus mexidol	—	Long-term stabilization of the pathological process with Traumeel
Ointment plus laser scalar	—	Effective disease stabilization with Traumeel
Ointment	—	Fewer foci and absence of pain in the Traumeel group

to placebo (solution without active components; n = 15) for 4 weeks. Immediate pain relief was reported after Traumeel administration. The WHO stomatitis score was significantly lower in patients receiving Traumeel than in those receiving placebo (10.4 vs 24.3; P < .01). The development (66% vs 93%, respectively) and worsening (47% vs 93%, respectively) of stomatitis also occurred less frequently in the Traumeel group than in the placebo group. The methodology of this study was well reported, but the randomization procedure was not adequately described (Jadad score = 4).

A nonrandomized study in 27 patients with chemotherapy-induced stomatitis showed a reduction in the duration of symptoms of mucositis in patients receiving Traumeel S injection as a mouth rinse compared to standard treatment.<sup>21</sup> Traumeel also resulted in rapid pain relief, occurring between 20 minutes and 2.5 hours after treatment.

**Corticosteroid-dependent Asthma Bronchiale.** In a randomized, controlled study, patients with corticosteroid-dependent asthma bronchiale of more than 5 years duration and treated with 4 to 8 mg/day of triamcinolon were found to benefit from treatment with Traumeel.<sup>22</sup> Patients were treated with Traumeel injection (Traumeel S, 1 ampoule every 5 to 7 days for 20 weeks; n = 71) or placebo (n = 32) in addition to basic treatment with cortisone and methylxanthine. When compared to baseline, spirometry results were improved and immunoglobulin (Ig) E levels were decreased in the Traumeel group. Moreover, while steroid demand was increased in placebo-treated patients, demand was reduced in patients receiving Traumeel. Shortcomings regarding the reporting of the study randomization and double-blind procedures resulted in a Jadad score of 3.

In a nonrandomized study, patients with severe corticosteroid-dependent asthma bronchiale (n = 50) were allocated to one of two groups: to receive standard treatment with steroid/methotrexate or standard treatment with steroid/cyclosporine.<sup>23</sup> Patients in each of these groups were then allocated to additionally receive Traumeel S injection plus Engystol N or placebo or no further treatment. This study suggested that the combination of Traumeel and Engystol may provide relief for patients with asthma bronchiale, as the greatest reduction in steroid demand was observed in patients also receiving this combination therapy.

**Tonsillectomy (Postoperative Treatment).** In a study of 80 patients with purulent tonsillitis, Traumeel S injection (1 ampoule/day intramuscularly; n = 40) or standard treatment (n = 40) was given after surgery.<sup>24</sup> After 5 days, patients receiving Traumeel S reported a significantly greater improvement in pain, as assessed using a VAS pain scale than patients on standard treatment (P = .04). Patients given Traumeel also found it easier to open their mouths the day after surgery and accepted food earlier than did placebo-treated patients.

### Constituents of Traumeel

Indications for the use of the constituents of Traumeel in phytotherapy and in micro- and ultra low dilutions are presented in Table 5.

***Aconitum napellus* (Aconite).** *Aconitum napellus* root has been widely used in traditional Asian medicine as a treatment for rheumatism and wounds, but it is not popular in modern Western phytotherapy. A prescription of *Aconitum* in micro- and ultra low dilutions is given in cases of violence and where sudden stress causes intense anguish. Signs attributed to *Aconitum* are erythema of the face, heat, flushing, and fever.

Analgesic effects of *Aconitum napellus* have been demonstrated in preclinical models.<sup>25</sup> In a double-blind, placebo-controlled clinical trial, microdilutions of *Aconitum* relieved postoperative pain and agitation in children.<sup>26</sup>

***Arnica montana* (Arnica).** *Arnica montana* is very popular in modern phytotherapy due to its analgesic, antibacterial, and antiinflammatory properties. The extracts are used for the topical treatment of a wide range of rheumatic conditions. The active ingredients are flavonoids, glycosides, and lactones. Micro- and ultra low dilutions of *Arnica* are indicated for the treatment of trauma and its associated symptoms, such as pain, swelling, and bruising. Specific assessments have confirmed the safety of microdiluted *Arnica* preparations.

Pooled results from double-blind, placebo-controlled studies suggested that treatment with *Arnica* C30 resulted in a greater reduction of muscle soreness immediately after a marathon run than placebo.<sup>27</sup> Information is not available on the superiority of one potency of *Arnica* to another. A review of all prospective, controlled trials investigating microdilutions of *Arnica* (68 comparisons in 49 clinical trials) observed significant treatment effects in patients with traumatic injuries in a random effect meta-analysis but not in meta-regression models.<sup>28</sup> The heterogeneity of the results might be a consequence of the inclusion of trials investigating *Arnica* as monotherapy and as an ingredient in complex preparations (ie, in combination with other ultra low-diluted remedies). Complex remedies contributed mainly to the positive assessment of *Arnica* in the random effect meta-analysis.

Ultra low dilutions of *Arnica* D6 have been shown to improve recovery after bilateral endoscopic carpal-tunnel release, significantly reducing pain compared with placebo.<sup>29</sup> Furthermore, a randomized, double-blind, placebo-controlled study in patients with varicose vein surgery (n = 60) showed a trend towards a beneficial effect of *Arnica* D12, in terms of reductions in postoperative hematoma and pain.<sup>30</sup> *Arnica* D30 treatment also resulted in a significantly larger reduction in pain score compared to placebo after tonsillectomy (n = 111).<sup>31</sup> In combination with ultra low dilutions of *Hypericum*, ultra low dilutions of *Arnica* were particularly effective in patients with dental-associated interventions and neuralgia.<sup>28,32</sup>

***Atropa belladonna* (Belladonna).** Due to toxicity, *A. belladonna* extracts are not used in modern phytotherapy. In micro- and ultra low dilutions, *A. belladonna* is indicated in the treatment of complaints with sudden onset and disappearance; in pain described as throbbing, sharp, cutting, shooting or burning; and in bright red or inflamed parts with intense burning or hyperesthesia. Ultra low dilutions of *A. belladonna* are

TABLE 5 Indications of Traumeel Constituents in Phytotherapy and in Micro- and Ultra Low Dilutions

Constituents	Phytotherapy	Micro- and Ultra Low Dilutions	Important Results From Clinical Studies With Micro- and Ultra Low Dilutions
<i>Aconitum</i>	Not used	Postoperative pain, analgesia	Relief of postoperative pain and agitation in children (double-blind, placebo-controlled study) <sup>26</sup>
<i>Arnica</i>	Topical treatment for rheumatic conditions	Trauma and trauma-associated symptoms	Lower muscle soreness with <i>Arnica</i> C30 (pooled results) <sup>27</sup> Less pain after tonsillectomy ( <i>Arnica</i> D30) <sup>31</sup>
<i>Belladonna</i>	Not used due to toxicity	Acute conditions characterized by inflammation and infection	Effective in acute dermatitis during radiotherapy for breast cancer <sup>33</sup> Significant reduction if migraine attacks (in combinations with other ultra low-diluted drugs) <sup>34</sup> Reduced frequency of recurrence of otitis media in pediatric patients <sup>35</sup>
<i>Bellis perennis</i>	Not established	Deep bruising, complaints after physical trauma, symptoms associated with rheumatism, hematoma	Reduction of postpartum bleedings (in combination with <i>Arnica</i> ; a placebo-controlled study) <sup>36</sup>
<i>Calendula</i>	Eczema, conjunctivitis, thrush infections, minor injuries, skin problems	Internal and external injuries where the skin is broken	Prevention of radiotherapy-related dermatitis (topical ointment; open comparison with tromoline, phytotherapeutic extract) <sup>37</sup> Greater reduction of ulcer surface (topical phytotherapeutic extract) <sup>38</sup>
<i>Chamomilla</i>	External use for wounds, sunburn, burn, hemorrhoids, mastitis, leg ulcers Internal use for nervous digestive upsets, insomnia, travel sickness	Sensitivity to every perception (eg, surroundings, people, pain)	Antiinflammatory effect was superior to placebo (ointment vs ointment base; phytotherapeutic extract) <sup>39</sup> More rapid decrease of weeping wound area (phytotherapeutic extract) <sup>40</sup>
<i>Echinacea</i>	Internal use for infections, early stages of cough and cold External use for herpes, acne, infected injuries	Similar indications as in phytotherapy	Significant decrease of symptoms of sinusitis (combined with other remedies in ultra low dilutions; compared to placebo) <sup>41</sup>
<i>Hamamelis</i>	Topical treatment for minor skin lesions, local skin inflammations, hemorrhoids, varicose veins	Venous bleeding, venous and varicose disorders	Noninferiority to bufexamac in atopic dermatitis (phytotherapeutic extract) <sup>42</sup> Reduction of cutaneous blood flow <sup>43</sup>
<i>Hepar sulfuris</i>	Not used	Inflammation, purulent processes after the highly acute phase	Monotherapy not investigated in clinical trials
<i>Hypericum</i>	Internal use for depressive mood disorders External use for wounds, burns, dermatitis, myalgia	Similar indications as in phytotherapy	Antiinflammatory (analgesic properties): improvement of eczematous lesions in patients with subacute dermatitis (phytotherapeutic extract) <sup>45</sup>
<i>Mercurius solubilis</i>	Not used	Infectious diseases of mouth and throat, edema, inflammation	Shorter duration of fever and fewer recurrences of otitis media in children <sup>35</sup>
<i>Millefolium</i>	Injuries, wounds	Cases with bright red bleeding	Not performed
<i>Symphytum</i>	Ulcers, colitis, rheumatism, psoriasis, eczema, injuries	Bone injuries, bone fractures (acceleration of callus formation)	Not investigated in micro- or ultra low dilutions

predominantly prescribed in acute conditions characterized by inflammation and infection.

Prospective clinical studies have investigated the efficacy of various ultra low dilutions of *A belladonna* in patients with acute radiodermatitis during radiotherapy for breast cancer, with migraine, and in children with acute otitis media. The double-blind trial in patients with acute radiodermatitis showed a trend towards greater efficacy of *A belladonna* 7CH compared to placebo, as assessed by a calculated severity index (the sum of the scores of four parameters, including breast skin color, warmth, swelling, and pigmentation).<sup>33</sup> The double-blind, placebo-controlled treatment of 60 patients with migraine with one or two of eight ultra low-diluted ingredients (*A belladonna*, *Ignatia*, *Lachesis*, *Silicea*, *Gelsemium*, *Cyclamen*, *Natrium muriaticum*, and *Sulphur*) resulted in a significant reduction of the periodicity, frequency, and duration of migraine attacks.<sup>34</sup> Additionally, a prospective comparison between several ultra low-diluted remedies as monotherapy (*Aconitum*, *Belladonna*, *Chamomilla*, *Mercurius solubilis*, *Pulsatilla*, *Silicea*; n=103) and conventional therapy (n=28) showed a reduced frequency of recurrence of acute otitis media in pediatric patients.<sup>35</sup>

***Bellis perennis* (Daisy).** *Bellis perennis* extract, traditionally used as a topical treatment for wounds, is not established in modern phytotherapy. In ultra low dilutions, *Bellis perennis* is used for the treatment of deep bruising, complaints after physical trauma, rheumatism-associated symptoms following overexertion, hernatoma, hemorrhage, and venous stasis.

A randomized, double-blind study compared the effects of ultra low dilutions of *Arnica* (10<sup>-6</sup>) and *Bellis* (10<sup>-60</sup>) with placebo in 45 patients with mild postpartum bleeding.<sup>36</sup> The mean baseline hemoglobin level was 12.7 g/dL in all treatment groups. Seventy-two hours postpartum, there was a greater reduction in the mean hemoglobin level of patients in the placebo group compared with patients in the two active treatments groups (11.6 g/dL vs 12.4 g/dL, respectively; P<.05).

***Calendula officinalis* (Marigold).** *Calendula* extracts are used externally for the treatment of eczema, conjunctivitis, thrush infections, minor injuries, and skin problems. Ultra low dilutions of *Calendula* are commonly used for the treatment of internally and externally injuries with skin damage.

A randomized, open-label, phase III trial presented preliminary evidence for *Calendula* ointment in the prevention of radiotherapy-related dermatitis.<sup>37</sup> Fewer patients using *Calendula* reported grade 2 to 3 skin toxicity compared to the control group using tromaline (41% vs 63%, respectively; P<.001). Additionally, a placebo-controlled trial in 34 patients with lower leg venous ulcers reported a mean reduction in ulcer surface area in 41.7% of patients using *Calendula* ointment compared to 14.5% in the control group.<sup>38</sup> Complete epithelialization of the ulcer area was observed in seven patients using *Calendula* vs four controls.

***Chamomilla* (Spec) (Chamomile).** In phytotherapy, *Chamomilla* is used externally for wounds, sunburn, burns, hemorrhoids, mastitis, and leg ulcers, and is taken internally for nervous digestive upsets, insomnia, and travel sickness. Ultra low

*Chamomilla* dilutions are indicated in patients who are sensitive to all things and sensations, such as to their surroundings, people, and pain.

In healthy volunteers with experimentally induced skin lesions, an ointment containing a 2% ethanol chamomile flower extract was reported to have a superior antiinflammatory effect compared to the ointment base alone.<sup>39</sup> A placebo-controlled, double-blind trial investigating the effect of an ethanol *Chamomilla* fluid extract was also conducted in 14 patients after dermabrasion. Cessation of weeping and complete drying of the wound occurred more rapidly in *Chamomilla*-treated patients compared to placebo (15.0±5.1 days vs 17.1±5.5 days, respectively).<sup>40</sup> There was no evidence that microdiluted *Chamomilla* as monotherapy had been investigated in clinical studies.

***Echinacea (angustifolia and purpurea)* (Purple coneflower).** *Echinacea* stimulates the immune system and has antiviral and antibacterial effects. In phytotherapy, *Echinacea purpurea* is taken internally for infections and early stages of coughs and colds. External preparations are used for conditions such as herpes, acne, and infected injuries. In ultra low dilutions, *E purpurea*, *E angustifolia*, and *E pallida* are used for the same indications as *E purpurea* in phytotherapy.

Clinical interest in *Echinacea* focuses on its immunomodulatory effects, such as the prevention and treatment of upper respiratory tract infections. Most studies demonstrated the superiority of *Echinacea* phytotherapy in the prevention and treatment of respiratory tract infections compared with placebo. Microdiluted *Echinacea* D1 in combination with other microdiluted remedies, including *Cinnabaris* D4, *Hydrastis* D1, and *Kalium bichromatum*, resulted in a significantly greater decrease in the sum score of five symptoms of sinusitis compared with placebo (-6.2 vs -1.7, respectively; P<.0001).<sup>41</sup>

***Hamamelis virginiana* (Witch Hazel).** Extract of *Hamamelis* is used topically for the symptomatic treatment of minor skin lesions, local skin inflammations, hemorrhoids, and varicose veins. *Hamamelis* at low potencies (D2) or as the mother tincture is used for treating venous bleeding and venous and varicose disorders.

In a randomized, double-blind study, no significant differences were observed in the outcomes of 22 patients with atopic dermatitis treated with standardized *Hamamelis* extract compared with bufexamac ointment.<sup>42</sup> The study drugs were administered simultaneously on both forearms of each patient, with the side for each treatment randomly selected. Independent of treatment, there was a clear improvement in symptoms. Other clinical investigations demonstrated that *Hamamelis* treatment reduced cutaneous blood flow, skin temperature, and ultraviolet-induced erythema.<sup>43</sup>

***Hepar sulfuris* (Hepar sulfuris calcareum) (Calcium sulfuratum Hahnemannii).** Samuel Hahnemann developed the use of micro- and ultra low dilutions of *Hepar sulfuris* mainly for the treatment of local inflammation and purulent conditions after the acute phase.

No clinical trials of *Hepar sulfuris* monotherapy were found in the literature search. As part of complex ultra low-diluted

remedies, *Hepar sulfuris* is effective at all stages of the inflammatory process, and it is particularly recommended for infectious diseases of the mouth and throat.

**Hypericum perforatum (St John's Wort).** *Hypericum* extracts are commonly used for the treatment of functional depressive mood disorders. Topical preparations are used for the treatment of superficial wounds, burns, dermatitis, and myalgia. Ultra low dilutions of *Hypericum* are used for similar conditions. Symptoms indicating the use of *Hypericum* are head congestion with irritation of the nervous system and wounds that are very sensitive to touch.

Clinical studies investigating the antiinflammatory and analgesic properties of *Hypericum* were reviewed only. In a double-blind study of 21 patients with subacute dermatitis, significantly greater improvement was observed in eczematous lesions following treatment with a cream containing *Hypericum* extract than after placebo (cream vehicle;  $P < .05$ ).<sup>44</sup>

**Mercurius solubilis Hahnemannii (Mercurius vivus).** *Mercurius solubilis* was presented by Hahnemann to provide a soluble form of *Mercurius*. *Mercurius solubilis* is often used for the treatment of infectious diseases of the mouth and throat and is used in low potencies where the condition is characterized by edema and inflammation.

A prospective observational study comparing several single remedies in micro- and ultra low dilutions with placebo found that children with otitis media treated with *Mercurius solubilis* had a shorter duration of fever and fewer recurrences of otitis media in the following year.<sup>35</sup>

**Achillea millefolium** (Yarrow). In traditional phytotherapy, *Achillea millefolium* is recommended for the treatment of injuries and wounds due to its antihemorrhagic, analgesic, and antiinflammatory properties. Clinical use in phytotherapy and in ultra low dilutions (recommended in cases with bright red bleeding) is based mainly on empirical evidence. Indications for the use of *Achillea millefolium* include traumas, injuries, gynecological complaints, circulatory disturbances, diaphoretic impairment, diseases of the urinary system, and functional intestinal complaints. No randomized, controlled clinical studies of *Achillea millefolium* were found in the literature search.

**Symphytum officinale** (Comfrey). *Symphytum officinale* has been used in phytotherapy for the treatment of internal diseases, such as ulcers, colitis, and rheumatism, and of external diseases, including psoriasis, eczema, and injuries. Currently, it is commonly used in sports medicine, particularly for the treatment of injuries of the ankle. In ultra low dilutions, the remedy is mainly used for the treatment of bone injuries and bone fractures to accelerate callus formation and the healing of fractures.

## Safety

**General Side Effects.** Hypersensitivity reactions have been observed in isolated cases with all Traumeel presentations, and local allergic skin reactions have been reported with Traumeel ointment and/or gel. In rare cases, systemic treatment with Traumeel may be associated an increase in the production of saliva.

**Healthy Volunteers.** In an open-label study investigating the safety of Traumeel, 36 mild-to-moderate, transient adverse events were observed in 11 out of 20 healthy volunteers receiving Traumeel tablets (6 tablets/day).<sup>45</sup> The most frequently reported events were headache ( $n=15$ ), diarrhea and stomach discomfort/bloating ( $n=6$ ), and nausea ( $n=3$ ). No event was considered definitely or probably related to Traumeel, and all events resolved without special intervention despite continuation of treatment.

**Traumeel Injection Solution.** In a randomized, clinical trial in patients with chemotherapy-induced mucositis, the side effect profile of patients treated with Traumeel S injection differed from patients receiving placebo.<sup>20</sup> A greater frequency of graft vs host disease, sepsis, and gastrointestinal complications were reported for the Traumeel group, while more venous-occlusive diseases and pneumonia were reported for the placebo group. The small number of study participants and severity of their illness prevented any definitive conclusions regarding the safety of Traumeel S injection. The tolerability of Traumeel S injection was rated as "good" or "very good" in the majority of patients in two observational studies: one study was in 184 patients with epicondylitis, the other was in 3241 patients with different orthopedic indications.<sup>13,18</sup>

**Traumeel S Ointment.** A multicenter drug monitoring study including more than 3400 patients confirmed that Traumeel S ointment is well tolerated.<sup>10</sup> Adverse events, including transient local irritation or allergic skin reactions, were observed in 13 cases only. Treatment was discontinued in three patients due to allergic reactions.

**Surveillance Studies.** The safety of all marketed application forms of Traumeel was reviewed in a large survey of over 3.6 million patients.<sup>46</sup> Adverse events were observed in only 0.0035% of cases. Most adverse events were mild skin reactions after application of Traumeel ointment and pruritus at the injection site after Traumeel injection, both of which disappeared after treatment discontinuation.

**Comparisons With NSAIDs.** An observational nonrandomized study, demonstrated the superior tolerability of Traumeel S injections compared with NSAID injections in 184 patients with epicondylitis.<sup>13</sup> In this study, tolerability was rated as "very good" in 87.7% of patients receiving Traumeel and 44.9% of patients administered NSAIDs.

**Constituents of Traumeel.** No data regarding the safety of ultra low dilutions of the constituents as used in commercially available Traumeel presentations were found in the literature search. Reported safety issues were restricted to their presentations as used in phytotherapy.

## DISCUSSION

This review presents the available evidence for the clinical efficacy of the multicomponent combination medication, Traumeel, and its constituents in a broad range of indications including contusions, fractures, epicondylitis, musculoskeletal complaints, tendinosis, and tendinopathy. In addition, the review details the suggested bioregulatory, immunomodulatory,

and antiinflammatory mode of action of Traumeel and its constituents. Altogether, six randomized, controlled studies; 19 nonrandomized, controlled studies; four cohort studies; and numerous case reports support the clinical use of Traumeel in these indications, while several controlled studies provide evidence of the activity of the constituents of Traumeel in their key indications.

### Mode of Action

Efficacy in various clinical indications suggests that Traumeel works in a different way compared to NSAIDs. In contrast to NSAIDs, Traumeel and its constituents do not directly influence the metabolism of arachidonic acid but exert bioregulatory effects via the inhibition of various proinflammatory cytokines, such as Interleukin (IL)-2, IL-6, and tumor necrosis factor-alpha (TNF- $\alpha$ ); modulation of regulatory T-cells/transforming growth factor-beta (TGF- $\beta$ ); and inhibition of IL- $\beta$ , IL-8, and TNF- $\alpha$  production. The reviewed data suggest strong immunomodulatory effects in at least two important therapeutic target systems: the ECM and regulatory T-cells.

### Acute Sport Injuries

In current clinical practice, Traumeel ointment is commonly used for the treatment of physical trauma and sport injuries. Its efficacy in these indications is supported by investigations with several of the constituents of Traumeel, which demonstrate the immunomodulatory, antiinflammatory, and analgesic effects of *Arnica montana*, *Calendula officinalis*, and *Chamomilla*, and by the comprehensive clinical trial program of this multicomponent medication, which includes randomized and nonrandomized studies. Two well-conducted randomized, placebo-controlled studies (Jadad score = 4) demonstrated a greater reduction in swelling and pain and improved mobility in patients treated with Traumeel S ointment compared to patients receiving placebo.<sup>5,6</sup> Additional trials presented evidence of noninferiority of Traumeel compared with NSAIDs, including diclofenac.<sup>13,15</sup> Moreover, these findings are supported by a multicenter drug-monitoring trial of more than 3000 patients treated under conditions of everyday routine clinical practice.<sup>10</sup> Investigators reported the efficacy of Traumeel to be "good" or "very good" in more than 80% of patients.

The most likely explanation for Traumeel's efficacy in the treatment of physical trauma and sport injuries is through the induction of ECM remodeling and tissue repair. Cutaneous wound healing begins with an alternating keratinocytes-ECM interaction at the wound edge, where cells migrating into the area are exposed to dermal collagen. Ultimately, this process results in changes in the ECM and the development of a more favorable environment for cell migration.<sup>47</sup>

There is also evidence for the role of Traumeel in the modulation of growth factor activity, which, after injury, results in skeletal muscle regeneration. Regeneration is regulated by fibroblast growth factor, platelet-derived growth factor, insulin-like growth factor, and TGF- $\beta$ , which have a major influence on

the reorganization of the cellular matrix. In models, TGF- $\beta$ 1 and TGF- $\beta$ 3, expressed by regenerating muscles during the first days after trauma, influence nearly all important processes for muscle regeneration.<sup>48</sup> These observations support the regulatory and immunomodulating effects of Traumeel during tissue regeneration after physical trauma and sport injuries. This theory is backed by preclinical studies suggesting that exogenous TGF- $\beta$  might promote the healing of acute and chronic wounds<sup>49</sup> and a phase II trial demonstrating a positive effect of topical TGF- $\beta$ 2 on diabetic foot ulcers.<sup>50</sup> Thus, improved TGF- $\beta$  signaling at least partly explains the efficacy of Traumeel in wound healing and tissue repair.

Findings of investigations regarding the constituents of Traumeel concur with those of the complete bioregulatory combination. *Arnica montana* reduced muscle soreness after a marathon run in a double-blind, placebo-controlled trial<sup>27</sup> and demonstrated a significant effect in patients with traumatic injuries in a meta-analysis.<sup>28</sup> Both *Calendula officinalis* and *Chamomilla* had effects on external injuries with skin damage, such as in radiotherapy-induced dermatitis (*Calendula*)<sup>37</sup> and dermabrasion (*Chamomilla*).<sup>40</sup> *Hepar sulfuris* and *Mercurius solubilis*, which are used mainly in multicomponent medications to increase the efficacy of the combination, might have broad antiinflammatory activity. Additionally, *Achillea millefolium* and *Symphytum officinale* have been used in traditional phytotherapy for the treatment of injuries and wounds, with *Symphytum officinale* being particularly commonly used in sports medicine.

Together, the evidence demonstrates the efficacy of Traumeel in the treatment of acute sport injuries, which may be attributed to its well-balanced composition of constituents.

### Hemarthrosis

Two placebo-controlled studies, one of which was randomized, support the use of intra-articular Traumeel injections in patients with hemarthrosis. The randomized study demonstrated the superiority of Traumeel injections on joint circumference and mobility, intensity of pain, and effusion volume vs placebo.<sup>11</sup> In the nonrandomized study, patients administered Traumeel injections showed a reduction of effusion compared to placebo and not one required a second aspiration.<sup>12</sup>

Several constituents of Traumeel have shown activity in bleeding-related disorders. *Bellis perennis* diminished postpartum bleeding in a double-blind, placebo-controlled study,<sup>36</sup> *Hamamelis* reduced cutaneous blood flow,<sup>43</sup> and *Arnica* D12 showed a trend towards a reduction of postoperative hematoma vs placebo.<sup>30</sup>

### Epicondylitis

Traumeel injections are at least as effective as NSAID injections in patients with epicondylitis; noninferiority on all evaluated variables was demonstrated by a well-conducted, nonrandomized multicenter study.<sup>13</sup> In this study, Traumeel was also significantly superior in relieving pain at rest and

improving joint mobility than NSAIDs. Global outcome as rated by patients was also more frequently rated as “good” or “very good” by the Traumeel group. These results suggest that Traumeel may be considered a valid alternative to NSAIDs for the symptomatic treatment of epicondylitis.

### Tendinosis and Fibromyalgia

While there is evidence for the efficacy of Traumeel in patients with tendinosis, the data are not definitive due to the nonrandomized nature of the two studies. One of these non-randomized studies showed that, compared to thermotherapy, patients treated with Traumeel injections had significantly improved pain relief, which was maintained after treatment discontinuation.<sup>14</sup> The observational study reported comparable improvements in mobility scores between Traumeel ointment and diclofenac gel.<sup>15</sup>

For patients with fibromyalgia, findings of a small double-blind, placebo-controlled study investigating Traumeel in combination with other medications with bioregulatory properties delivered in micro- or ultra low doses are promising.<sup>16</sup> Patients benefited from significant reductions in muscular pain, although the results should be interpreted with caution due to few participating patients ( $n=20$ ) and methodical shortcomings (Jadad score=1).

### Rheumatoid Arthritis

The efficacy of Traumeel in the treatment of rheumatoid arthritis was suggested in preclinical investigations, which demonstrated antiinflammatory effects ranging from the inhibition of proinflammatory cytokines, such as IL-2, IL-6, and TNF- $\alpha$ , to the modulation of regulatory T-cells. Results of an open-label, nonrandomized, pilot study in patients with rheumatoid arthritis support preclinical findings regarding the immunomodulatory action of Traumeel.<sup>17</sup> However, the observed changes in regulatory T-cells in patients were not unidirectional because increases as well as decreases were reported, all of which need to be confirmed in more rigorous and investigative clinical trials.

### Chemotherapy-induced Mucositis

The antiinflammatory and immunomodulatory effects of Traumeel in patients with chemotherapy-induced mucositis were demonstrated in a randomized, well-conducted study (Jadad score=4)<sup>20</sup> and a nonrandomized study.<sup>21</sup> Efficacy in this indication might be explained by inhibition of proinflammatory cytokines (IL-1 and TNF- $\alpha$ ) at the start of mucositis, the tissue-protecting properties of some of the Traumeel constituents further in the course of the disorder, the antibacterial effects of some constituents during ulceration, and the bioregulatory effects supporting skin regeneration during healing.

### Asthma Bronchiale

Two studies investigated patients with corticosteroid-dependent asthma bronchiale, a severe atopic disorder charac-

terized by airway hyper-reactivity and airway remodeling as result of T helper (Th)-2 cell responses in the lung. Treatment with Traumeel was associated with a reduced demand for steroids and improved lung function.<sup>22,23</sup> These effects might reflect the induction of bioregulatory processes, such as the equalization of Th-1 cells, Th-2 cells, and regulatory T-cells and their responses. However, these results and the effects on T-cells need to be confirmed in further clinical studies.

### Tonsillectomy (Postoperative Treatment)

A controlled study demonstrated that recovery after tonsillectomy was improved when patients were administered Traumeel compared to standard treatment.<sup>24</sup> This observation is supported by several studies investigating the constituents of Traumeel, including *Arnica* D12 for postoperative pain,<sup>20</sup> *Arnica* D30 given posttonsillectomy, and *Aconitum napellus* in postoperative pain and agitation in children.<sup>26</sup>

### Traumeel as an Alternative to NSAIDs

Traumeel has been shown to be as equally as effective as NSAIDs in the treatment of patients with various sport-related injuries. In an observational study in patients with acute and chronic tendinopathies, the reduction in pain and improvement in mobility was comparable between the Traumeel and NSAID groups.<sup>15</sup> Similar results were also observed after local Traumeel S injections and intramuscular NSAID injections in patients with epicondylitis.<sup>13</sup> These observations were confirmed by a recently published double-blind study (not included in the analysis).<sup>51</sup> In this study, a significantly superior reduction in pain was reported for elite athletes with nontraumatic tendinous pain treated with Traumeel S ointment compared with diclofenac ointment and with placebo ointment.

### Safety

Despite the impact of Traumeel on various immunological processes, the available evidence from clinical studies demonstrates that this multicomponent combination medication is well tolerated. Spontaneous adverse event reporting during more than 60 years of Traumeel use in clinical practice suggest an excellent safety profile. There are no indications in which there is an increased risk of hypersensitivity or allergic reactions with therapy. Monotherapy with micro- and ultra low dilutions of all constituents have also proven to be well tolerated in clinical practice. Moreover, the tolerability of Traumeel, in terms of the number and frequency of adverse events, is reported to be significantly improved when compared with NSAIDs.<sup>13</sup>

### CONCLUSIONS

There is mounting evidence supporting the clinical efficacy of the bioregulatory drug, Traumeel, in the treatment of patients with acute or subacute musculoskeletal problems, such as trauma and sport injuries. The observed efficacy of Traumeel may be credited to the immunomodulatory, antiinflammatory, and analgesic effects provided by the well-balanced combination of its

constituents. Traumeel's efficacy and excellent safety profile warrant its consideration as a first-line treatment of physical trauma and sport injuries and as an alternative to NSAIDs.

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