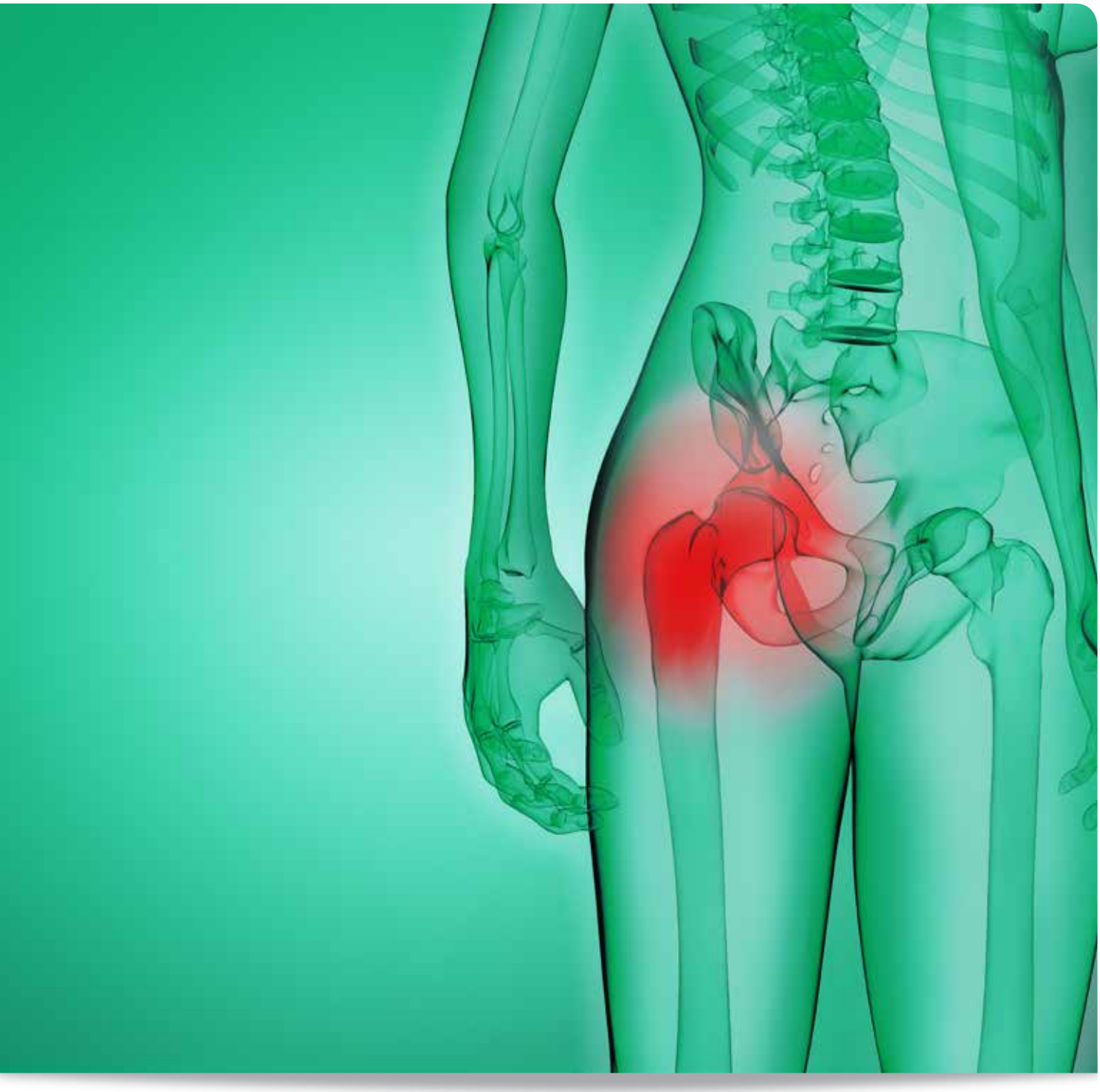
Product Monograph



Zeel® T

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Contents

Zeel® T

1 Overview

Zeel® T has been researched for over 40 years, and has been used extensively by patients in over 30 countries. Each year, almost one million patients are treated with Zeel® T worldwide.

Degenerative joint disorders (DJDs), such as osteoarthritis (OA), are common and debilitating conditions that can have numerous causes and etiologies. Conventional medical treatments are supported by a reasonable evidence base, but are associated with limitations to their use, eg, adverse effects and restrictions for long term use. Zeel® T offers patients with OA and rheumatic joint diseases a natural alternative to conventional treatments without their associated side effects and limitations. The recent MOZArT study, a large randomized controlled trial, demonstrated that the co-administration of intra-articular injections of Traumeel® and Zeel® T is effective in reducing the pain associated with osteoarthritis of the knee (see Section 5).[1]

Several studies with Zeel® T demonstrate its excellent efficacy, safety and tolerability in degenerative joint disorders.[2–5] Furthermore, patient satisfaction with treatment effectiveness with Zeel® T is high.[3,5]

There are no known drug interactions, very few contraindications and adverse events are extremely rare with Zeel® T. Zeel® T can be used with confidence in patients taking other medications, and in those with concomitant conditions, such as hypertension, cardiovascular disease, gastrointestinal disturbances and kidney disease. Zeel® T is suitable for acute and longer-term use. It can be safely combined with natural or conventional treatments[3,4] but is effective as monotherapy.[2–5]

In vitro and animal studies point to a multi-targeted mechanism of action for Zeel® T mediated by its various ingredients that involves chronic inflammation,[6–8] prevention of vascularization of the cartilage and endochondrium,[9,10] remodeling and protection of cartilage[11–13] and alteration to cartilage mechanics[14] (see Section 4). The multi-targeted action of Zeel® T, and the inclusion of plant products in its formulation, supports a therapeutic potential in close alignment with recent understanding of the immunopathogenesis of OA, suggesting that there needs to be "development of more novel approaches to treat OA, which may include therapies that act on multiple targets. Plant natural products have this kind of property and may be considered for future drug developments."[15]

Zeel® T contains several active ingredients (14 in the ampoules for injection, and 15 in the tablets and ointment (see Section 3).

Zeel® T is available in three different formulations – solution for injection, ointment and tablets. These different formulations maximize convenience and flexibility of use. The exact indication and dosage of the Zeel® T formulations can be found on the country-specific package inserts.

Zeel® T offers an effective, safe and well-tolerated natural treatment in osteoarthritis and rheumatic joint diseases.

2 Therapeutic indications

The therapeutic indication for the Zeel® T formulations is:

- Osteoarthritis and rheumatic joint diseases.

3 Composition

There are three formulations of Zeel® T – ampoules for injection, ointment and tablets. Their respective compositions, including quantity and excipients, are shown below.

	Zeel® T ampoules for injection		Zeel® T Ointment		Zeel® T Tablets	
Active and inactive ingredients	*Dilution*	*Quantity per 100g*	*Dilution*	*Quantity per 100g*	*Dilution*	*Quantity per 100g*
Acidum DL-alpha liponicum	D8	0.09 g	D6	0.010 g	D6	0.01 g
Arnica montana	D4	9.09 g	D2	0.300 g	D1	0.20 g
Cartilago suis	D6	0.09 g	D2	0.001 g	D4	0.10 g
Coenzym A	D8	0.09 g	D6	0.010 g	D6	0.01 g
Embryo totalis suis	D6	0.09 g	D2	0.001 g	D4	0.10 g
Funiculus umbilicalis suis	D6	0.09 g	D2	0.001 g	D4	0.10 g
Nadidum	D8	0.09 g	D6	0.010 g	D6	0.01 g
Natrium diethyloxalaceticum	D8	0.09 g	D6	0.010 g	D6	0.01 g
Placenta totalis suis	D6	0.09 g	D2	0.001 g	D4	0.10 g
Rhus toxicodendron	D2	0.45 g	D2	0.270 g	D2	0.18 g
Sanguinaria canadensis	D4	0.14 g	D2	0.225 g	D3	0.15 g
Solanum dulcamara	D3	0.45 g	D2	0.075 g	D2	0.05 g
Sulfur	D6	0.16 g	D6	0.270 g	D6	0.18 g
Symphytum officinale	D6	0.45 g	D8	0.750 g	D8	0.05 g
Acidum silicicum	-	-	D6	1.000 g	D6	1.00 g
Sodium chloride	-	0.80 g	-	-	-	-
Water for injections	-	79.43 g	-	-	-	-
Cetostearyl alcohol (type A), emulsifying	-	-	-	8.01 g	-	-
Ethanol 96% (V/V)	-	-	-	9.57 g	-	-
Paraffin, liquid	-	-	-	9.34 g	-	-
White soft paraffin	-	-	-	9.34 g	-	-
Water, purified	-	-	-	60.81 g	-	-
Lactose monohydrate	-	-	-	-	-	97.25 g
Magnesium stearate	-	-	-	-	-	0.5 g

4 Mechanism of action

In vitro and animal studies point to a multi-targeted mechanism of action for Zeel® T mediated by various ingredients of Zeel® T that involves:

- Chronic inflammation[6,7,8]
- Prevention of vascularization of the cartilage and endochondrium[9,10]
- Remodeling and protection of cartilage[11,12,13]
- Alteration to cartilage mechanics.[14]

Chronic inflammation

KEY FACT

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

i. Overview

The effects of sub-clinical chronic inflammation in OA are now increasingly being recognized.[16] The onset of acute inflammation is generally sudden, with symptoms (redness, warmth, swelling and further loss of function) developing in a matter of minutes or hours. Neutrophils are the most abundant cells, and pro-inflammatory cytokines, such as IL-1 and TNF-α, are the most prominent. In the development of OA, the pro-inflammatory cytokines, IL-1, TNF-α·, IL-6 and other members of the IL-6 protein superfamily, such as IL-7, IL-17 and IL-18, have all been shown to be associated with cartilage damage and, therefore, the development of OA.[15,17,18]

In contrast, chronic inflammation develops over a longer period of time and may persist for weeks, months or years. Markers of chronic inflammation, such as C-reactive protein (CRP), may be elevated in patients with OA, and may be mediated by IL-6, which is the major cytokine secreted by macrophages.[19]

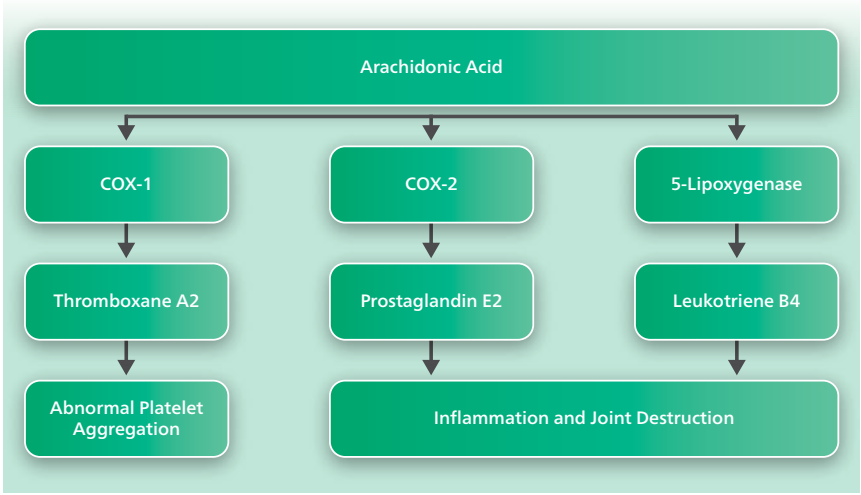
IL-6 may also play a role in angiogenesis, which is another factor contributing to the pathology of OA.[20,21]

The outcome of acute inflammation is elimination of the irritation, followed by restoration of the tissues to their original state. However, in chronic inflammation, inflammation and repair occur concurrently, and the joints remain abnormal even after the inflammation subsides. In addition in chronic inflammation, the cells that predominate are macrophages and often lymphocytic infiltrates. Chronic inflammation can, therefore, be seen as a misguided attempt on the part of chondrocytes and other cells to eliminate damaged tissue and to effect repair.

Several enzymes, e.g., cyclo-oxygenase (COX) and lipoxygenase (LOX) – are catalysts for reactions, producing mediators of inflammation and pain. COX enzymes are responsible for the production of lipid mediators, including prostaglandins, prostacyclin and thromboxanes (Figure 1). There are two main isoforms of COX: COX-1 is expressed in most cells, and COX-2 is induced by pro-inflammatory agents (such as cytokines).[22] The majority of prostaglandin E2 (PGE2) is synthesized from arachidonic acid in cells by COX-2 enzymes and terminal prostaglandin E synthases.[23,24] PGE2 is a potent vasodilator, causing fluid to leak from blood vessels into the surrounding tissue and resulting in swelling. It is a principal mediator of inflammation and pain.[23,25]

LOX enzymes are responsible for the production of leukotrienes, which are lipid signalling molecules synthesized from arachidonic acid. An example is LTB4 which is synthesised by the 5-LOX enzyme. This is a powerful chemo-attractant for leukocytes (white blood cells),[26] and is implicated in the pathogenesis of inflammation.

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



KEY FACT

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.

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.[27]

Traditionally, non-steroidal anti-inflammatory drugs (NSAIDs) have been used to manage arthritic pain. They work by blocking the activity of COX enzymes. Early NSAIDs (such as naproxen) were non-selective and inhibited both COX-1 and COX-2. However, the inhibition of COX-1, which is expressed widely throughout the body and makes prostaglandins that protect the stomach and kidney from damage,[22] is thought to be responsible for the majority of the adverse effects seen with the non-selective NSAIDs. Subsequently, NSAIDs that were more selective for COX-2 (such as celecoxib and valdecoxib) were developed.

However, inhibition of COX enzymes by NSAIDs is associated with increased 5-LOX activity. Because they share the same substrate (arachidonic acid), inhibition of COX pathways results in increased substrate availability for 5-LOX, leading to a shift towards leukotriene production.[6] This increased leukotriene production has been implicated in the development of stomach ulcers,[28] as well as increased spasms of smooth muscles of airways and associated vasculature and therefore, increased risk of asthmatic attacks.[29,30]

Furthermore, leukotriene B4 (LTB4) in particular is elevated in chronic inflammatory joint diseases, such as rheumatoid arthritis, and has been implicated in the chronic inflammation and joint destruction associated with this disease.[30]

In contrast to NSAIDs and COX-2 inhibitors, Zeel® works by modulating both the 5-LOX and COX-1 and -2 pathways (see below).[6] Such dual inhibition would be expected to relieve pain and inflammation whilst avoiding further gastrointestinal damage.[31] The dual inhibition prevents the shift towards active production of leukotrienes with further gastrotoxic effects[30] that occurs with inhibition of COX alone.

Following prostaglandins/ thromboxanes	→	no inflammation or pain (minimal loss of gastroprotection)
Following leukotrienes	→	no further damage to gastric mucosa (or no active damage to gastric mucosa)

ii. Study demonstrating the dual inhibition of COX/LOX by Zeel®

The inhibitory activity of Zeel® on LOX and COX pathways was investigated in an *in vitro* study.[6]

Jäggi 2004[6]

Objective

- This *in vitro* study examined the ability of Zeel® and its constituents to inhibit the synthesis of LTB4 by 5-LOX, and inhibit the synthesis of PGE2 by COX-1 and COX-2.

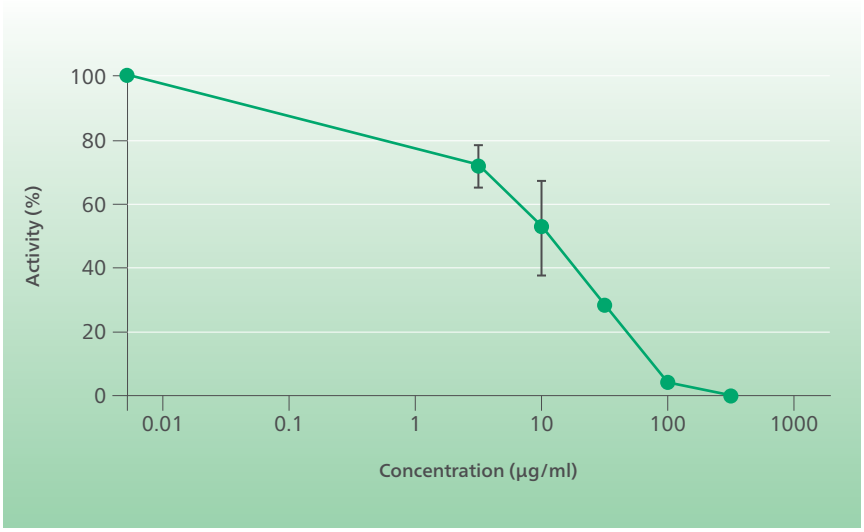
Methods

- The effect of Zeel® on the 5-LOX pathway was assessed by incubation with a human cell line, followed by an enzyme-linked immunoassay to measure LTB4 production.
- The effect of Zeel® on the COX pathway was assessed by incubation with purified COX-1 and COX-2 enzymes, as well as in a human cell line, followed by enzyme-linked immunoassay to measure PGE2 production.
- The half maximal inhibitory concentration (IC50) value measured how much Zeel® is needed to inhibit each enzyme. Potent inhibition was indicated by a low IC50 value.

Results

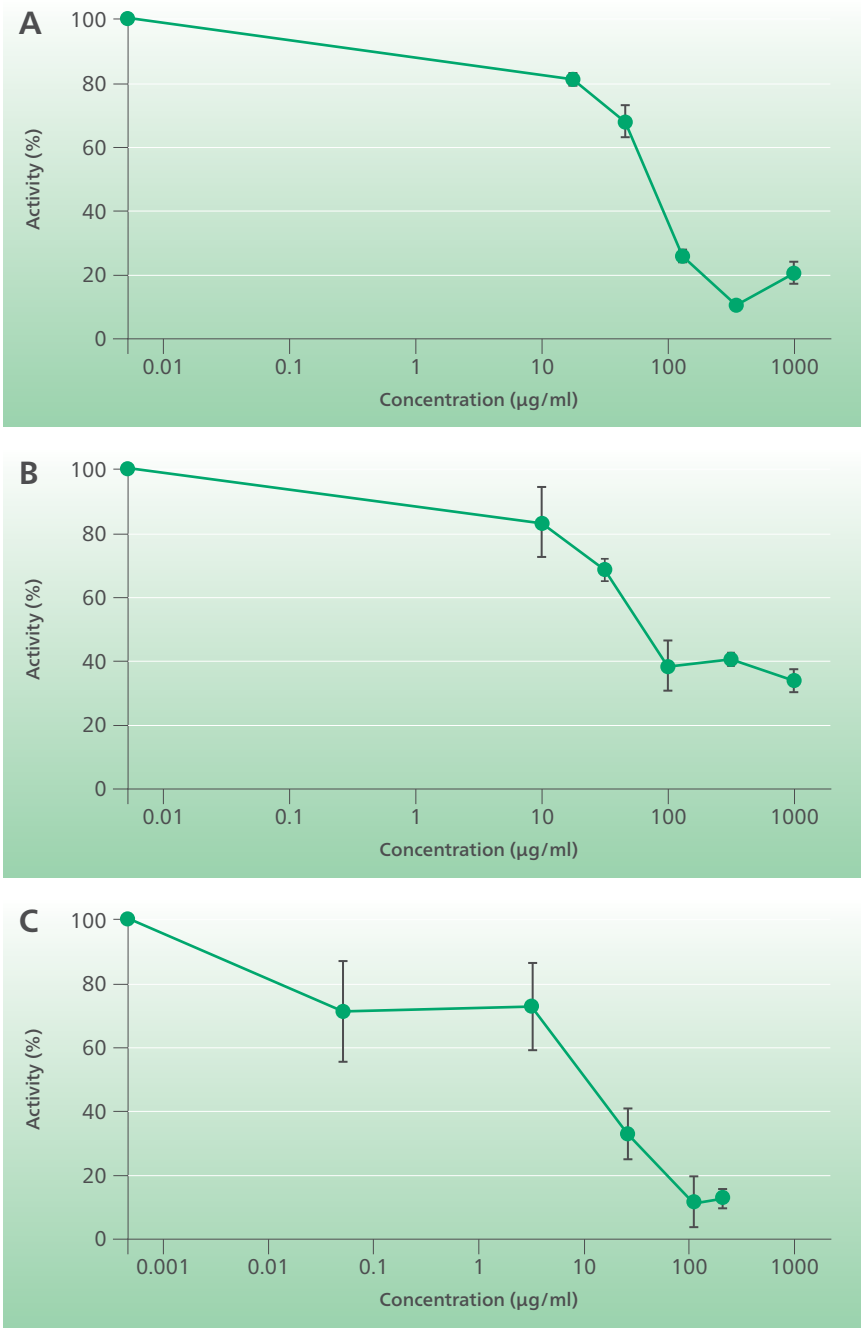
- Zeel® inhibited LTB4 production with an IC50 value of 10 µg/mL (Figure 2).

Figure 2
Inhibition of LTB4 production (modulation of 5-lipoxygenase) by Zeel® in cellular 5-LOX assay.[6]



- Zeel® inhibited PGE2 production by purified COX-1 (IC_{50} 50 µg/mL) and COX-2 (IC_{50} 60 µg/mL) enzymes, as well as inhibiting PGE2 production in the cellular assay (IC_{50} 10 µg/mL) (Figure 3).

Figure 3
Inhibition of PGE2 production by Zeel®: A) modulation by COX-1 enzymes, B) modulation by COX-2 enzymes, C) simultaneous modulation of COX-1 and COX-2.[6]



- Some of the individual constituents of Zeel® inhibited the synthesis of LTB4 by 5-LOX, including extracts of *Arnica montana* (at IC_{50} value of 20 µg/mL), *Sanguinaria canadensis* (IC_{50} 2 µg/mL) and *Rhus toxicodendron* (IC_{50} 5 µg/mL). Sulphur also inhibited LTB4 by approximately 45% at the level tested.
- Some of the individual constituents of Zeel® inhibited PGE2 production by COX:
  - PGE2 production by purified COX-1 enzymes was inhibited by *Arnica montana* (IC_{50} 80 µg/mL), *Sanguinaria canadensis* (IC_{50} 40 µg/mL), *Rhus toxicodendron* (IC50 20 µg/mL) and *Solanum dulcamara* (IC_{50} 40 µg/mL).
  - PGE2 production by purified COX-2 enzymes was inhibited by *Arnica montana* (IC_{50} 110 µg/mL), *Sanguinaria canadensis* (IC_{50} 50 µg/mL), *Rhus toxicodendron* (IC_{50} 20 µg/mL) and *Solanum dulcamara* (IC_{50} 150 µg/mL).
  - Extract of *Solanum dulcamara* did not inhibit LTB4 synthesis.

Key points
- This *in vitro* study confirmed the dual inhibition of LOX-5 and COX (COX-1 and COX-2) pathways by Zeel®.
- The constituents of Zeel® – *Arnica montana*, *Sanguinaria canadensis* and *Rhus toxicodendron* – each individually inhibit both LOX-5 and COX (COX-1 and COX-2).
- *Solanum dulcamara* inhibits COX (COX-1 and COX-2, albeit relatively weakly) but does not inhibit LOX-5.

iii. Study demonstrating effect of Solanum dulcamara on prostaglandin biosynthesis

Solanum dulcamara is one of the components of Zeel®. An *in vitro* study has demonstrated the effect of this constituent on prostaglandin biosynthesis.[8]

Tunon 1995[8]

Objective
- To evaluate the activity of *Solanum dulcamara* on prostaglandin biosynthesis and platelet activating factor (PAF)-induced exocytosis *in vitro*.

Methods
- Extracts were tested *in vitro* for activity on prostglandin biosynthesis and effect on PAF-induced exocytosis using chemical assays.

Results
- *Solanum dulcamara* inhibited prostaglandin biosynthesis producing a strong inhibition of PAF-induced exocytosis.

Key points
- *Solanum dulcamara* extract has been demonstrated to contain anti-inflammatory effects based on inhibitory activity on prostaglandin biosynthesis and PAF induced exocytosis.

Zeel® T

Prevention of vascularization of the cartilage and endochondrium

KEY FACT

Sanguinarine (SA), an alkaloid isolated from the root of *Sanguinaria canadensis*, and one of the constituents of Zeel®, is known for its anti-angiogenetic effects by suppressing basal and VEGF-induced new vessel growth.

i. Overview of angiogenesis and chronic inflammation

The formation of new blood vessels is essential during fetal development but rarely occurs in adults, except in overzealous attempts at remodeling and regeneration, as in OA. Inflammatory mediators can stimulate angiogenesis either directly or indirectly. Inflammatory cells that produce this effect include macrophages and mast cells, which are present in the OA synovium. Macrophages are generally found wherever abnormal angiogenesis occurs, for example, in synovitis and tumors. Angiogenesis may be important in potentiating or perpetuating inflammation, rather than initiating it.

On the other hand, angiogenesis may be indirectly self-perpetuating because it increases inflammatory cell infiltration and thus increases the cells that secrete angiogenic factors, such as VEGF and Fibroblast Growth Factor (FGF-1).[20,21]

Vascularization of normally avascular cartilage and at the osteochondral junction is a feature of OA. In growing individuals, angiogenesis is required for normal endochondral ossification to close long bones. This process is mediated by VEGF from hypertrophic chondrocytes. In osteoarthritis, however, growth through osteophytes at the joint margin also occurs through osteochondral ossification. Cartilaginous extensions of the articular surface become invaded by blood vessels, and bone extends from the sub-chondral structures.[20]

The fact that Zeel® is formulated to address these aspects, along with its excellent tolerability, makes it an ideal option for treating the chronic inflammation seen in OA.

Sanguinarine (SA), an alkaloid isolated from the root of *Sanguinaria canadensis*, and one of the constituents of Zeel®, is known for its anti-angiogenetic effects by suppressing basal and VEGF-induced new vessel growth.

Studies demonstrating effect of Sangiuinaria canadensis on VEGF

Basini 2007[9]

Objective

- To evaluate the possible effect of Sangiuinaria (300 nM) on Akt phosphorylation in a porcine aortic endothelial cell line.

Methods

- Akt activity was evaluated using an ELISA-based assay that uses a synthetic peptide as a substrate for protein kinase B (PKB) and a polyclonal antibody that recognizes the phosphorylated form of the substrate.

Results

- The alkaloid, Sangiuinaria, significantly ($p<0.001$) inhibited the VEGF-induced Akt increase.

Key point

- These data suggest that Sangiuinaria may represent an antiangiogenic agent by completely abolishing VEGF-induced Akt phosphorylation.

Basini 2007[10]

Objectives

- To evaluate the effects of Sanguinarine in an *in vitro* angiogenesis model.

Methods

- SA (300 nM) was tested in the presence or absence of VEGF (100 ng/ml) in a three dimensional angiogenesis bioassay obtained pipetting a suspension of porcine aortic endothelial cells on microcarrier beads in a fibrinogen solution before the addition of thrombine. Endothelial cell proliferation was measured at 48, 96, 144, 192 h.

Results

- The addition of Sanguinarine abolished ($p<0.001$) VEGF stimulatory effect on AOC growth at all the examined times.

Key point

- Sanguinarine appears to be an antiangiogenic natural product by directly suppressing the proliferative effect of VEGF on endothelial cell line. This effect could be mediated by blocking the VEGF-induced Akt activation.

Remodeling and protection of cartilage

i. Overview

The articular cartilage covering the ends of bones in joints provides a low friction surface for motion and distributes the load applied to the joint. Cartilage is comprised of chondrocytes (cartilage-forming cells) and an extracellular matrix. In this, a collagenous network (made of collagen) is responsible for the matrix's tensile strength, and proteoglycans (proteins that have carbohydrates attached to them) are responsible for the osmotic swelling and elastic properties of cartilage tissue.[32]

KEY FACT

In osteoarthritic joints, the extracellular matrix of the cartilage degenerates, undergoing biochemical and structural alterations.

In osteoarthritic joints, the extracellular matrix of the cartilage degenerates,[33] undergoing biochemical and structural alterations.[34] Degradation of the cartilage and progressive failure of its biomechanical properties ensues. As the cartilage degenerates, its ability to function deteriorates. Oscillation between degradation and repair is a normal occurrence in the matrix. Although the extracellular matrix is the functional unit in this process, homeostasis is affected by chondrocytes. Matrix metalloproteinases (MMPs) are stimulated by inflammatory cytokines and matrix degradation products to induce degradation of older or damaged tissues. These are counterbalanced by a number of growth factors, notably also members of the TGF-β family, Bone Morphogenetic Proteins (BMPs), which reciprocally inhibit the actions of the MMPs and, therefore, induce tissue healing. This catabolic/anabolic oscillation is of vital importance in normal tissue integrity.[35,36]

When the process is disturbed (due to continuous tissue damage, either by mechanical stressors or toxins) or the body's ability to trigger repair reduced (due to either a deficiency of growth factors or an inability to respond to them, as is seen in old age), an overactive catabolic/anabolic cycle results.

To better understand cartilage destruction, at least inasmuch as it is mediated by chondrocytes themselves (sometimes called chondrocytic chondrolysis), we must study the molecular mechanisms that disrupt the balance between chondrocyte catabolic and anabolic activity. Since chondrocytes are lost to cell death at some point in the process of cartilage destruction, it is also important to know whether these molecular factors also contribute to cell death.

The cause of chronic synovitis in OA is not well understood. Debris or parts of cartilage may be found in the synovium, where they provoke typical responses to foreign bodies. Mechanical injury to cartilage can also lead to the production of free radicals including reactive oxygen species (ROS).[37,38]

Transforming growth factor beta (TGF-β,) is a protein that controls proliferation, cellular differentiation and other functions in most cells. In fact, the synthesis of TGF-β, is one of the most important mechanisms controlling inflammatory reactions in the tissues due to its inhibition of cells of the immune system that are pro-inflammatory.[12]

ii. Studies demonstrating stimulation of TGF-β, in whole blood cultures with *Cartilago suis*[11,12]

Schmolz 2000/Schmolz 2001[11,12]

Objective

- To evaluate the modulatory activities on the release of TGF-β, of various natural compounds, including *Cartilago suis*, in human whole blood cultures.

Results

- Pronounced effects were observed by *Cartilago suis* on TGF-β; it was able to stimulate the release of this mediator several-fold.

Key point

- *Cartilago suis* strongly stimulates TGF-β, in whole blood cultures. With the central role of TGF-β, in immunomodulation, and tissue remodelling this is an important finding.

Agents that are able to halt, prevent or reverse cartilage damage have been described as chondroprotective. Well known examples include glucosamine and chondroitin, although demonstrating their clinical benefit in randomized controlled trials continues to prove elusive.[39] Zeel® may have a beneficial effect on cartilage mechanics.

iii. Study demonstrating chondroprotection in experimental osteoarthritis[13]

Stanãíková 1999[13]

Objective

- To assess the effect of Zeel® solution for injection on markers of osteoarthritis of the knee (gross morphology of medial condyles) (histology of medial and lateral femoral condyles).

Methods

- A total of 12 rabbits underwent anterior cruciate ligament transection of the right knee and simple arthrotomy of the left knee.
- They were randomly divided into two groups for treatment of osteoarthritic right knee:
  - 6 received intra-articular injection of Zeel® solution for injection
  - 6 received intra-articular injection of saline (control group)
  - Injections commenced immediately after surgery, then twice weekly for 9 weeks
- Left knees of all the rabbits received saline (serving as sham control; overall control group).

Results

- Gross morphology of medial condyles at 9 weeks:
  - The severity of right knee cartilage damage was generally lower in the Zeel® solution for injection group in comparison with the saline control group. Gross morphological grading of cartilage damage

showed a significantly lower extent of damage in the Zeel® solution for injection group
    - The gross morphological examination of left (sham control) knees revealed very few or no changes
- Histology of medial and lateral femoral condyles at 9 weeks:
    - The saline controls showed degenerative changes of the right knee articular cartilage including: rough surface, loss of superficial layer, erosion, fissures, irregular arrangement and form of chondrocytes
    - In the Zeel® solution for injection group, there were only limited signs of cartilage degeneration of femoral condyles
    - Mean global histopathological score in the Zeel® solution for injection group was significantly lower in medial condyles (20.70 ± 0.64) in comparison with the saline control group (23.40 ± 0.54, $p<0.05$). Similar results were observed in the lateral condyles.

Key point

- In a rabbit model of knee osteoarthritis, intra-articular injection of Zeel® solution for injection twice weekly for 9 weeks resulted in a significant and substantial decrease in severity of damage.

Alteration to cartilage mechanics

i. Overview

In osteoarthritic cartilage, decreases in elasticity and strength have been observed,[40] with softening, fibrillation and ulceration.[41] The elasticity of collagen decreases, and this is associated with a decreased ability of the cartilage to store elastic energy during movement.[40] Changes in the viscoelastic behaviour of cartilage are evident very early in the osteoarthritic process.[42]

ii. Study demonstrating the effect of Zeel® on cartilage mechanics in osteoarthritis

An *in vitro* study suggests that treatment with Zeel® results in increases in the elasticity of osteoarthritic cartilage.[14]

Weh 1990[14]

Objective

- This *in vitro* study investigated the mechanical properties of osteoarthritic cartilage treated with Zeel®.

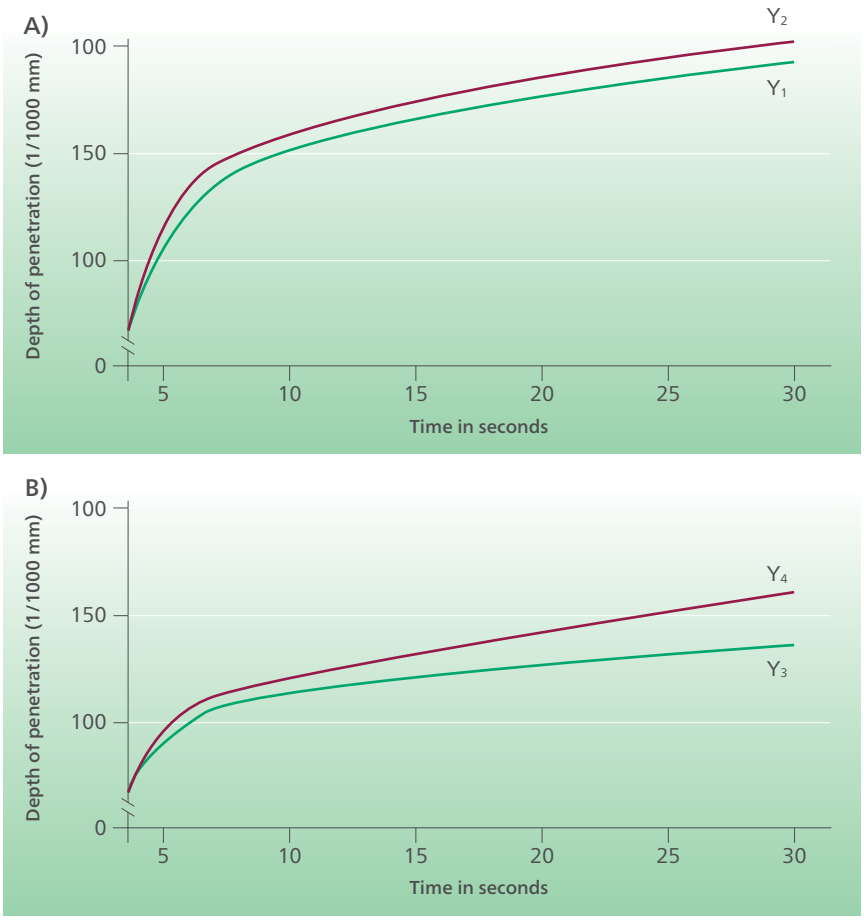
Method

- Cartilage samples were obtained from the joints of patients undergoing joint replacement surgery.
- The indentation hardness (elastic ductility) of the cartilage samples was tested before and after soaking in Zeel® solution for injection:
  - Half the samples served as controls, while the remainder were soaked in Zeel® for 12 days.
  - A device was used to measure hardness, involving the depth of penetration of a 5mm ball.

Results

- Cartilage samples soaked in Zeel® showed a mean 18% increased depth of penetration compared with baseline, whereas controls improved by a mean of 6% (Figure 4).

Figure 4
Depth of penetration of a 5mm ball for A) control cartilage and B) cartilage soaked in Zeel®[14]



Y1 and Y3 are the measurements taken at baseline; Y2 and Y4 are the measurements taken on day 12.

Key point

- This *in vitro* study showed that Zeel® appears to improve the mechanical properties of osteoarthritic cartilage by increasing its elasticity.

Summary of the multi-targeted mechanism of action of Zeel®

In vitro and animal studies point to a multi-targeted mechanism of action for Zeel® T that involves chronic inflammation,[6,7,8] prevention of vascularization of the cartilage and endochondrium,[9,10] remodeling and protection of cartilage[11,12,13] and alteration to cartilage mechanics.[14]

The constituents of Zeel® T act in a complementary manner to effectively relieve symptoms and improve the mechanical properties of cartilage.

5 Osteoarthritis

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.[43] 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.[44,45] 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.[46,47]

KEY FACT

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

The Framingham Osteoarthritis study demonstrated that radiographic evidence of OA increased with age, from 27% in patients younger than age 70, to 44% in patients age 80 or older. There was a slightly higher prevalence of radiographic changes of OA in women than in men (34% versus 31%); however, there was a significantly higher proportion of women with symptomatic disease (11% of all women versus 7% of all men; $p = 0.003$).[48]

In a re-evaluation of the Framingham OA study, the authors concluded that in the elderly, new onset of knee OA is frequent and is more common in women than men. However, among the elderly, age may not affect new disease occurrence or progression.[49]

Pharmacological treatments for OA include analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular (IA) injections of steroids and IA injections of viscosupplementation of hyaluronic acid (HA).[50] Topical preparations, including capsaicin and NSAIDs, can also be used.[51] The supplements chondroitin sulfate and glucosamine are also commonly used by patients despite a lack of evidence for effectiveness.[39]

Guidelines recommend oral or topical NSAIDs for the initial management of osteoarthritis, and they are commonly used in practice.[51,52,53]

In a network analysis, comparison of the most commonly used pharmacologic interventions for knee OA-related pain at 3 months, the conclusions reached where that all treatments except acetaminophen showed clinically significant improvement in pain. The authors stated that IA treatments were more effective than oral NSAIDs for pain, which is possibly due to the contribution of the integrated IA placebo effect.[54]

Drawbacks of current treatments

Several retrospective analyses have concluded that non-selective NSAIDs pose an increased risk of gastrointestinal adverse events (AEs).[55–59]

In general, these analyses have looked at patients undergoing long-term chronic therapy often with underlying inflammatory diseases such as OA.

Intra-articular injection of corticosteroids is also a common treatment for osteoarthritis of the knee, however, clinical evidence suggests that the benefit is short-lived, usually one to four weeks.[60] Additionally, concern has been expressed that long-term treatment could promote joint destruction and tissue atrophy.[60]

KEY FACT

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 data from clinical trials of viscosupplement products available in the public domain utilized heterogeneous methodologies and endpoints, and comparisons are therefore relatively difficult to interpret. These products appear to provide, at best, consistently moderate symptom improvement of OA knee pain despite the fact that viscosupplementation is universally used at a very significant cost. Improvements are often directional, and even when statistically significant, may not exhibit clinical endpoint effect sizes consistent with clinically relevant outcomes. Systematic reviews have provided confusing results. One concluded that IA HA has not been proven clinically effective and may be associated with a greater risk of AEs,[61] while a more recent 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.[54]

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.[1]

Traumeel® has been proven effective in the treatment of acute musculoskeletal injury and inflammation.[62,63] As well as providing an anti-inflammatory action, the components of Traumeel® act to modulate the effects of inflammation on body tissues. Thus, Traumeel® not only reduces inflammation, but it relieves pain and bruising and promotes healing after injury.For more information please refer to the Traumeel® Product Monograph.

The combination of Traumeel® and Zeel® T is a multi-ingredient, multi-target immunomodulation product that principally influences cytokines and TGF-β to attenuate cellular immunity while enhancing bone and cartilage formation.

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)[64]
- Angiogenesis (formation of new blood vessels)[64]
- Joint degradation (alteration in cartilage structure)[64]

The MOZArT study demonstrates that the intra-articular co-administration of Traumeel® /Zeel® T can reduce the pain associated with chronic moderate-to-severe knee osteoarthritis.[1] For more information please refer to the monograph on Osteoarthritis of the Knee: a new effective treatment option with Traumeel® and Zeel® T injections.

KEY FACT

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

Zeel® T

6 The evidence base – clinical efficacy, safety and tolerability

Several clinical trials with Zeel® T have demonstrated its excellent efficacy, safety and tolerability, and ability to improve symptoms in arthrosis/osteoarthritis and/or rheumatic joint diseases. The clinical evidence base supporting Zeel® T is detailed in the following pages.

Zeel® T solution for injection for arthritis in various joints

Reference: Lesiak A, Gottwald R, Weiser M. Skutecznosc kuracji preparatem Zeel T w iniekcjach dostawowych okolostawowych i domiesniowych w chorobie zwyrodnieniowej stawow. *Medycyna Biologiczna* 2001;kwiecień czerwiec zeszyt 2:30–36.[2]*

Study design:	Observational study
Formulation:	Zeel® T solution for injection
Indication(s):	Arthritis

Study design

- 523 patients with arthritis (71% female, 29% male). Arthritis of the knee (53%), vertebra (30%), hip (29%), shoulder (13%), finger (7%), ankle (6%), other (5%)
  - Duration of disease 1–10 years (38% >5 years)
  - All patients received Zeel® T solution for injection (intra-articular, peri-articular or intramuscular)

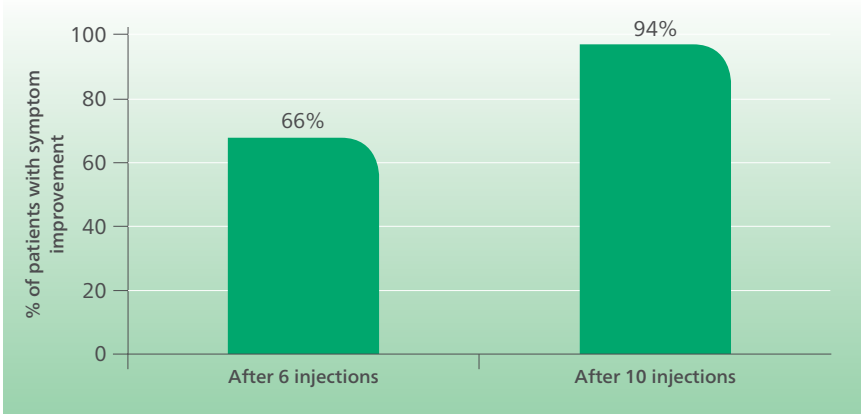
End points

- Symptom improvement
- Satisfaction with treatment, according to patient and physician

Results – efficacy

- Time to first improvement in symptoms
  - During the first 6 injections for two thirds of patients (Figure 5)
- Significant improvement in symptoms
  - After 10 injections for 94% of patients (Figure 5)

Figure 5
Percentage of patients with symptom improvement over time.[2]



* Lesiak A, Gottwald R, Weiser M. Effectiveness of the treatment of degenerative joint disease with periarticular, intraarticular and intramuscular injections of Zeel T. Biological Medicine 2001;2:30–36.

Results – safety
- No safety findings were reported in the English abstract.

Results – tolerability
- No tolerability findings were reported in the English abstract.

Conclusions
- Intra-articular, peri-articular or intramuscular injection of Zeel® T solution for injection improved the symptoms significantly in patients with arthritis in various joints.
- 94% of patients with arthritis in various joints experience significant improvement in symptoms after 10 injections of Zeel® T solution for injection.
- Two thirds of patients with arthritis in various joints experience improvement in symptoms within the first 6 injections of Zeel® T solution for injection.

Zeel® T solution for injection for osteoarthritis of the knee

Reference: Gottwald R, Weiser M. Treatment of osteoarthritis of the knee with Zeel® T. *Medicina Biológica* 2000;13(4):109–113.[3]

Study design:	Observational cohort study
Formulation:	Zeel® T solution for injection
Indication(s):	Osteoarthritis of the knee

Study design

- 100 patients with osteoarthritis of the knee
  - 78% female; 68% >60 years of age; 55% overweight
  - 58% had concomitant diseases, notably hypertension, osteoporosis, diabetes mellitus and ischemic cardiomyopathy
  - 69% had a duration of osteoarthritis >2 years
  - One knee per patient was included in the study
    - When both knees were affected, the one which caused the most pain was included in the study
    - 12% of patients had two knees affected
  - The cause of osteoarthritis was wear and tear (81%), congenital dysplasia (22%), joint deformity (14%), endogenous disorders (8%) and other (11%)
  - 91% patients had received prior treatment
    - Medical (16%), physical (7%) or both medical and physical (68%)
    - Medical treatment included non-steroidal anti-inflammatory drugs (NSAIDs), chondroprotectives and corticosteroids; physical treatment included electrotherapy, balneotherapy and therapeutic exercise
- Treatment
  - All patients received peri-articular injection of Zeel® T solution for injection
  - Twice weekly injections were planned, and were achieved in 86% of patients
  - In 71% of cases, 1 ampoule of Zeel® T solution for injection was injected each time
  - Duration of treatment was predominantly 4–6 weeks (58%)
  - Most patients received Zeel® T solution for injection as monotherapy (72%)
    - Where concomitant therapy was used, this was usually physical therapy (68%) rather than a medical (28%) or combined medical and physical therapy (4%)

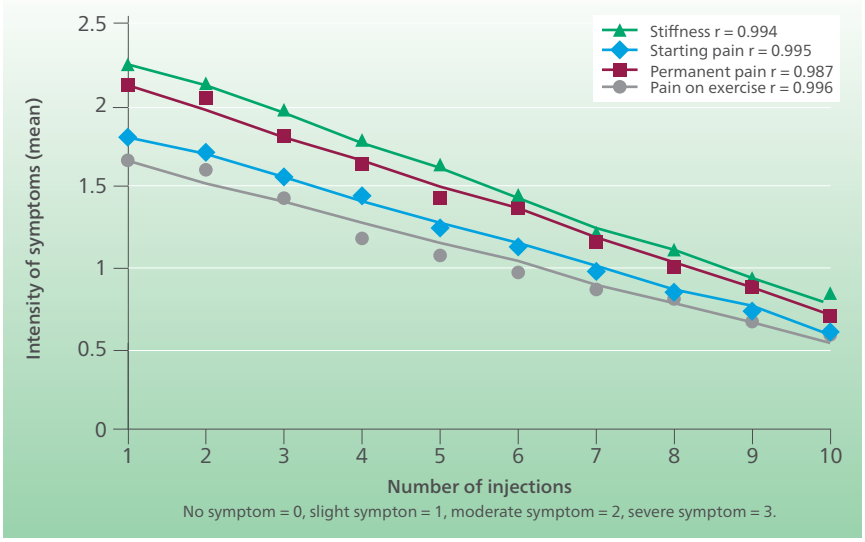
End points

- Intensity of symptoms
  - Stiffness, starting pain (pain upon onset of movement), pain on exercise and permanent pain
    - 4-point rating scale: 'none', 'slight', 'moderate', 'severe'
    - Assessed at baseline and before each injection
  - Time to symptom improvement
  - Treatment effectiveness
  - Patients and investigators assessed the efficacy of the treatment according to a 5-point rating scale: 'very good' (no more complaints), 'good' (significant improvement), 'moderate' (slight improvement), 'without success' (no change) or 'deterioration'.
- Tolerability
  - Patients and investigators assessed tolerability according to a 4-point rating scale: 'very good', 'good', 'moderate' or 'bad'.
- Adverse effects

Results – efficacy

- • Intensity of symptoms
  - At baseline, patients reported pain on exercise (97%), starting pain (92%), stiffness (74%), permanent pain (67%) and other (34%)
  - At baseline, symptom intensity was 'slight' (9%), 'moderate' (32%), 'severe' (36%) or 'very severe' (19%), with no data available in 4% of patients
  - During the first 10 injections, the intensity of symptoms decreased with each injection in a linear fashion (Figure 6)
    - Correlation coefficients demonstrated a direct correlation between the number of injections and improvement in symptom intensity (Figure 6)

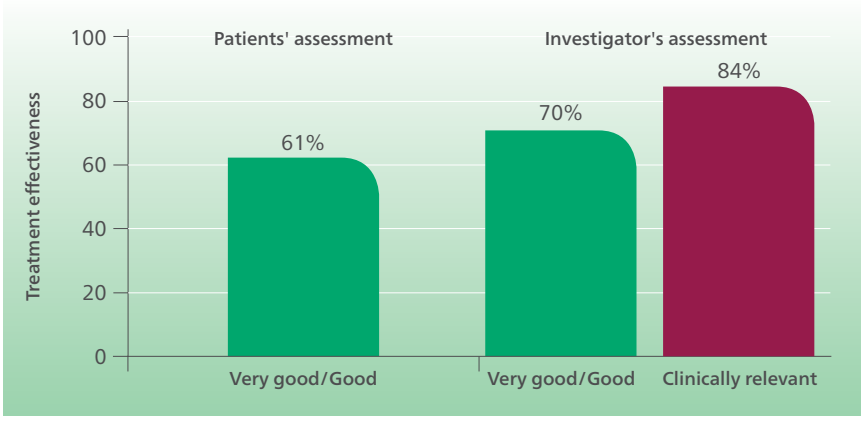
Figure 6
Change in the intensity of symptoms during 10 injections of Zeel® T solution for injection, with correlation coefficients for change in symptoms and the number of injections.[3]



Time to symptom improvement

- A significant improvement in symptoms was reported in 89% of patients
  - The time to first significant improvement in symptoms was between 2–5 injections for 67% of patients
  - 89% of patients reported a significant improvement after 10 injections
- Treatment effectiveness (Figure 7)
  - Assessed by investigators to be clinically relevant in 84% of cases, and being 'very good' (23%), 'good' (47%) or 'moderate' (19%)
  - Assessed by patients to be 'very good' (24%), 'good' (37%) or 'moderate' (24%)

Figure 7
Assessment of treatment effectiveness by investigators and patients.[3]



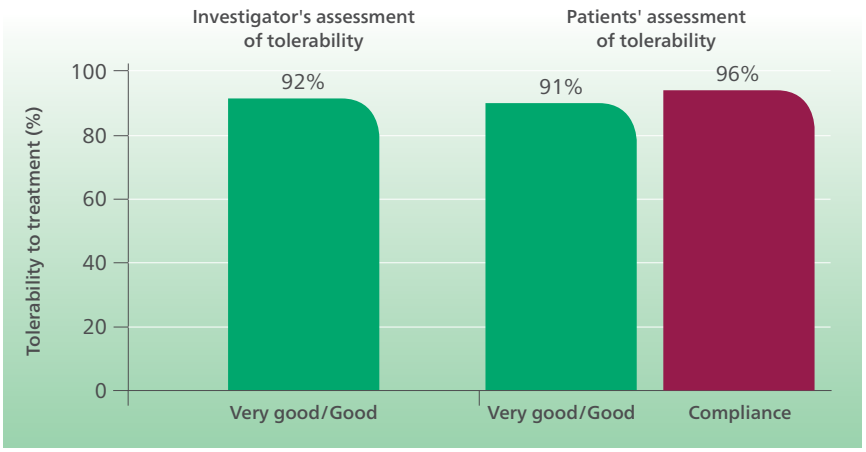
Results – safety

- Adverse effects were reported in 2 patients who complained of a painful injection procedure.

Results – tolerability

- Compliance was excellent, with 96% of patients completing the treatment according to the protocol.
- Tolerability was assessed by investigators as being 'very good' (79%) or 'good' (13%), with no data available in 8% of patients (Figure 8).
- Tolerability was assessed by patients as being 'very good' (65%), 'good' (26%), 'moderate' (6%) or 'bad' (1%), with no data available in 2% of patients (Figure 8).

Figure 8
Assessment of tolerability to treatment by investigators and patients.[3]



Conclusions

- In patients with osteoarthritis of the knee, peri-articular Zeel® T solution for injection (mostly as monotherapy) resulted in a progressive reduction in symptom intensity that was usually evident after 2–5 injections in patients who had tried previous treatments.
- Zeel® T solution for injection resulted in clinically-relevant treatment effectiveness in 84% of patients with knee osteoarthritis.
- The tolerability of Zeel® T solution for injection in patients with knee osteoarthritis was determined by investigators to be 'very good' or 'good' in 92% of cases.

Zeel® T ointment for degenerative articular disorders

Reference: Wodick RE. Steininger K, Zenner S. The biological treatment of articular affections – results of a study conducted with 498 patients. *Biologische Medizin* 1993;3:127–135.[4]

Study design:	Prospective, multi-centre cohort study
Formulation:	Zeel® T ointment
Indication(s):	Degenerative articular disorders

- 498 patients with degenerative articular disorders
  - 56% male, 44% female; mean age 42.9 years (±15.4 years)
  - Mean disease duration 18.8 months
  - Population comprised
    - Monarthrosis 49%, for whom the most frequent symptom was unilateral gonarthrosis (129/243), followed by hip, ankle, shoulder
    - Polyarthrosis 10%, including knee, hip, ankle, shoulder, finger
    - Spondylarthrosis 11%, most frequently in the lumbar spine, then cervical spine
    - Periarthropathia humeroscapularis 15%
    - Other degenerative articular disorders 15%
- All patients received Zeel® T ointment
  - There were no stipulations for the manner and frequency or duration of application
  - Frequency of application was once daily (n=32), twice daily (n=76), three times daily (n=262), four times daily (n=102), or five times daily (n=3) (23 not specified)
  - Application techniques varied
    - 52% received Zeel® T ointment without ointment dressing or iontophoresis, 8% with dressing, 11% by iontophoresis, and 29% with a combination of application types
  - Adjuvant therapies were permitted
    - 76% received Zeel® T ointment as monotherapy, 12% with Zeel® P injection, 9% with Zeel® tablets, and 3% with both Zeel® P injection and Zeel® tablets
  - Concomitant therapies were permitted
    - 32 patients took concurrent medication, including non-steroidal anti-rheumatics, anti-inflammatories, corticosteroids, local anaesthetics, vitamin preparations and homeopathic remedies
    - 78% of the patients underwent concurrent physical therapies, including kinesitherapy (50%), cryotherapy (37%), electrotherapy (34%), massage (20%), balneotherapy (16%)

End-points

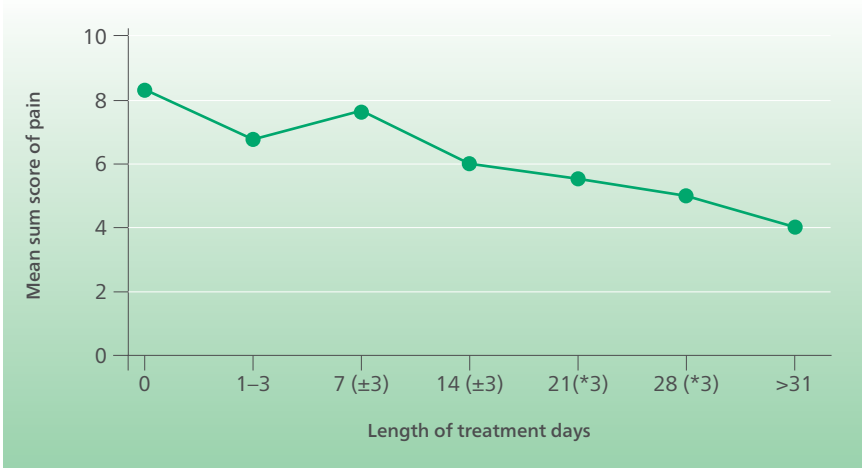
- Pain intensity
  - Scores for night pain, pain upon onset of movement (starting pain) and pain during movement
    - 1='no pain', 2='slight' pain, 3='moderately severe' pain, and 4='severe' pain
    - Addition of individual pain scores to create sum score
  - Measured at baseline and at up to three points during therapy (which varied for each patient), and categorised as:
    - 1st evaluation date: immediately before beginning of therapy
    - 2nd evaluation date: day 1-3
    - 3rd evaluation date: day 7 ± 3
    - 4th evaluation date: day 14 ± 3
    - 5th evaluation date: day 21 ± 3
    - 6th evaluation date: day 28 ± 3
    - 7th evaluation date: any time after day 31
- Investigator's overall assessment of the result of therapy ('very good', 'good', 'moderate' or 'poor')
- Investigator's overall assessment of tolerability ('very good', 'good', 'moderate' or 'poor')
- Adverse effects

Results – efficacy

Pain intensity

- Overall, pain intensity decreased with treatment (Figure 9)
  - There was no impact of adjuvant treatment with other the Zeel® preparations or the other concomitant therapies

Figure 9
Mean sum score of pain (night pain + starting pain + movement pain) for all patients (n=498).[4]



- The proportion of patients with 'severe' or 'moderately severe' night pain, starting pain and movement pain decreased with Zeel® T ointment
  - By the fourth evaluation date, the proportion of patients with 'severe' or 'moderately severe' pain was less than half that observed at baseline (Table 1)
  - By the fifth evaluation date, the proportion of patients with 'severe' or 'moderately severe' pain was approximately a quarter of that observed at baseline (Table 1)

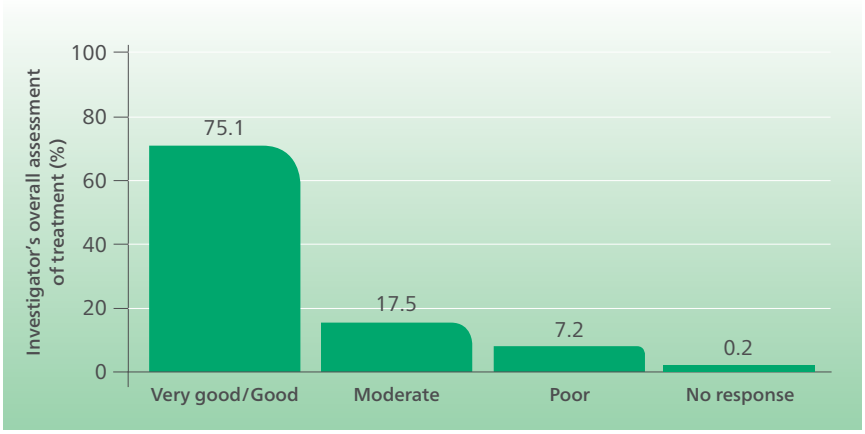
Table 1
Proportion of patients with 'severe' or 'moderately severe' pain.[4]

Time when pain assessed	Before beginning of treatment	Day 1–3	Day 7 (±3)	Day 14 (±3)	Day 21 (±3)	Day 28 (±3)	After Day 31
Types of pain	Percent share referenced to the patients respectively examined						
Night pain	42.9	19.8	31.8	17.5	10.7	5.0	–
Movement pain	89.9	54.9	63.8	38.3	24.7	20.0	–
Starting pain	65.4	42.4	43.1	23.5	16.2	5.0	–

The percent data were calculated with reference to the number of cases for which specific values were available on the respective dates.

- Investigator's assessment of overall result of therapy was 'very good' or 'good' in 75% of cases (Figure 10). Therapeutic success was achieved in 93% of patients.

Figure 10
Investigator's overall assessment of treatment (n=498).[4]



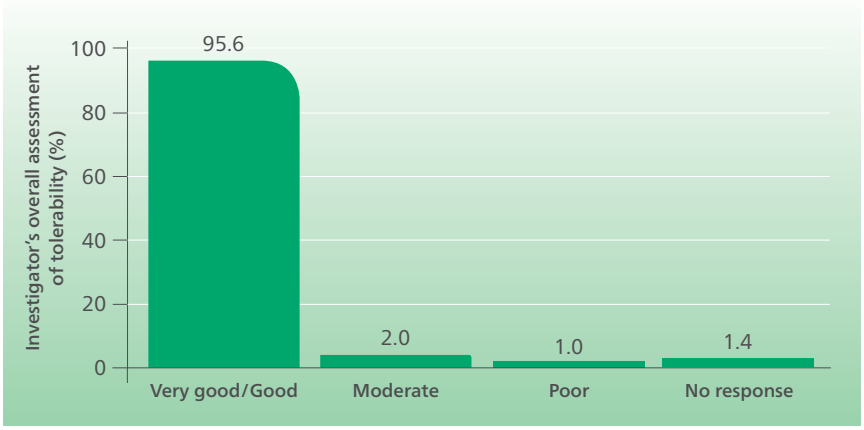
Results – safety

- A total of 20/498 patients (4%) reported adverse effects, of which 8 cases were considered probably related to application of Zeel® T ointment; 11 were considered to be of questionable causality, and 1 to be highly improbable
  - They included local skin irritations and allergic reactions to the preparation which were associated with symptoms, such as redness of the skin, itching, burning and, in some cases, the formation of vesicles or pustules. In 2 patients, there was also a report of burning during iontophoresis
  - No therapeutic measures of any kind were required for 8 of the patients; for the other cases, the adverse effects were effectively handled with systemic measures, or local administration of antihistamines and/or cooling
  - The intensity of the adverse effects was characterized in 10 cases as 'slight', in 7 cases as 'moderately severe' and in 3 cases as 'severe'

Results – tolerability

- Investigators rated tolerability as 'very good' (75%), 'good' (21%), 'moderately good' (2%) or 'poor' (5 patients); 7 cases were not rated (Figure 11)

Figure 11
Investigator's overall assessment of tolerability (n=498).[4]



Conclusions

- Patients with degenerative articular disorders treated with Zeel® T ointment experienced a reduction in night pain, starting pain and pain on movement, and the treatment was generally well tolerated
- The overall result of Zeel® T ointment treatment was rated as 'very good' or 'good' by investigators in 75% of patients with degenerative articular disorders.

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

Reference: Lozada C, del Rio E, Reitberg D et al. A multi-center double-blind, randomized, controlled trial (db-RCT) to evaluate the effectiveness and safety of co-administered Traumeel® (Tr14) and Zeel® (Ze14) intra-articular (IA) injections versus IA placebo in patients with moderate-to-severe pain associated with OA of the knee. *Arthritis Rheumatol* 2014; 66(suppl):S1266. Abstract no. 2896.[1]

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

Study design

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

End points

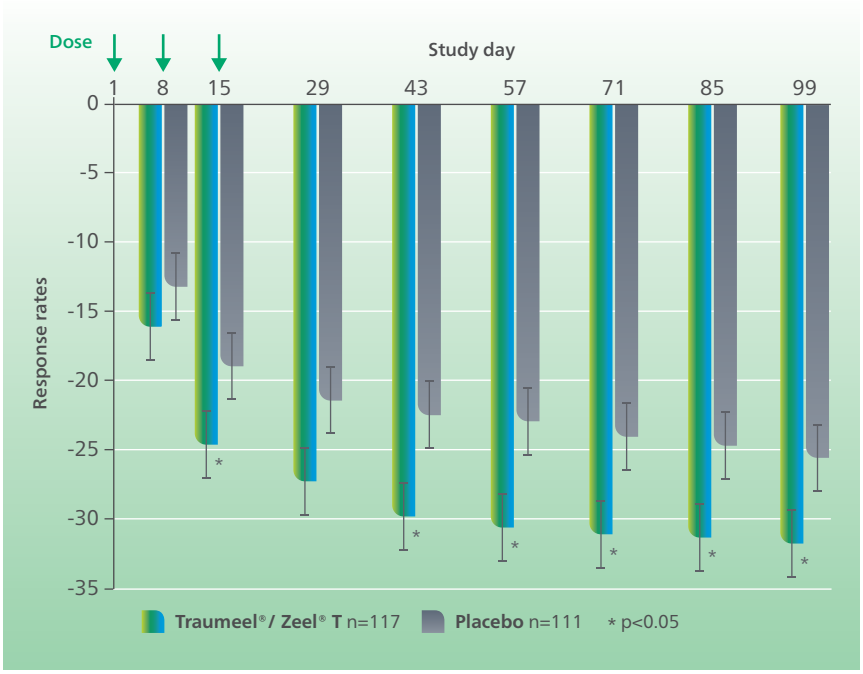
- Primary endpoint
  - Change in knee pain from Baseline to End-of-Study (Week 17) as measured by the WOMAC* OA Pain Subscale (Section A, 1–5) 100 mm VAS
- Secondary endpoints
  - Total WOMAC and sub scores for stiffness (B), and physical function (C)
  - Change in pain following a 50 ft walk (100 mm VAS)
  - Consumption of rescue medication
  - Patient and physician global assessments.
- Clinical relevance was assessed by comparing proportions of patients with reductions from baseline in WOMAC A scores greater than a validated benchmark Minimal Clinically Important Difference (MCID). This was chosen as -32.6 mm (the most conservative value) based on a study of outpatients with knee or hip OA where WOMAC VAS MCIDs ranged from -7.9mm to -32.6mm.[65]
- Safety was assessed by monitoring of vital signs, physical examinations of the target knee, adverse events and concomitant medications.

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

Results

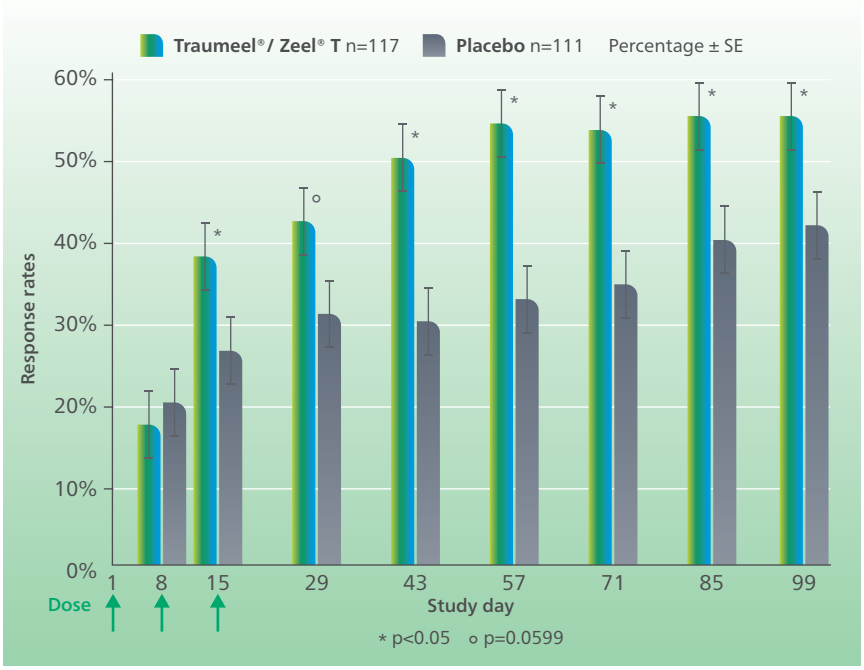
- Treatment arms were well balanced across demographic and baseline characteristics.
- The combination Traumeel®/Zeel® T started to be significantly different ($p<0.05$) for WOMAC A Pain already after the second of 3 injections on Day 15 and was subsequently significantly different on Days 43, 57, 71, 85 and 99 (primary endpoint day) (Figure 12).[66]
- Effect sizes compared with placebo were 0.26, 0.22, 0.30, 0.31, 0.30, 0.25 and 0.25 for Days 15, 29, 43, 57, 71, 85 and 99, respectively, indicating persistent efficacy over time with values comparable or superior to independently reported intra-articular and oral treatment.[54,66]

Figure 12
Mean (± SE) changes from baseline in WOMAC A (Knee Pain Subscale) (Intention-to Treat).[66]



- The proportion of patients achieving a MCID response with Traumeel®/ Zeel® T was significantly greater ($p<0.05$) already after the second of 3 injections on Day 15 and was subsequently significantly different on Days 43, 57, 71, 85 and 99 (primary endpoint day) (Figure 13).[1]
- 50' walk pain was similarly discriminating as was the physician global assessment.
- Total WOMAC and subscores B&C were directionally consistent with WOMAC A.
- There were no related SAEs. AEs were generally mild and unrelated to treatment. Local knee-related AEs, lab assessments, ECGs and vital signs were unremarkable and similar between treatments.
- Periodic Safety Update Reports/Development Safety Update Reports confirmed a favorable safety profile; Traumeel® exposure was at least 117,333,284 ampoules or 2,257,043 Pt-years with cumulative 7 serious and 39 non-serious possibly-related ADRs; Zeel® T was at least 30,168,795 ampoules or 580,169 Pt-years with a cumulative 0 serious and 9 non-serious ADRs.[66]

Figure 13
Percentage of patients achieving decrease in WOMAC Pain subscale score of ≥ 32.6 mm from baseline (Intention-to-Treat).[1]



Conclusion

- The co-administered intra-articular injection of Traumeel® and Zeel® T provided statistically significant and clinically relevant pain relief on days 15 to 99 in comparison to placebo.
- In this double-blind, randomized, controlled trial, a biological/mineral multi-component combination was shown to be a safe and effective treatment for pain in moderate-to-severe knee OA.
- Efficacy effect sizes were consistent with those observed for intra-articular hyaluronic acid, intra-articular corticosteroid and oral NSAIDs.[54,66]
- Unlike oral NSAIDs, the safety profile was benign with no signals of cardiovascular, gastrointestinal or other concerning risks.[66]
- From a qualitative perspective, the risk-benefit relationship for Traumeel® and Zeel® T appears favorable, particularly compared to oral NSAIDs.[54,66]

7 Pharmaceutical information

Contraindications
Known allergy (hypersensitivity) to one or more of the ingredients. Do not use during pregnancy and lactation.

Side effects
- Zeel® T ampoules for injection and tablets
  - Allergic (hypersensitivity) skin reactions may occur in very rare cases (i.e. affects less than 1 in 10,000 users).
- Zeel® T ointment
  - None have been reported.

Pregnancy and lactation
Do not use during pregnancy and lactation.

Overdose
No cases of overdose have been reported, and none are expected due to the homeopathic dilutions.

Special warnings and special precautions for use
- Zeel® T ampoules for injection
  - None.
- Zeel® T ointment
  - Cetylstearyl alcohol may cause local skin reaction s (e.g. contact dermatitis). Avoid contact with eyes, mucosae, open wounds or broken skin.
- Zeel® T tablets
  - Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Interaction with other medicaments and other forms of interaction
No interactions have been reported, and none are expected due to the homeopathic dilutions.

Effects on ability to drive and use machines
- Zeel® T ampoules for injection and tablets
  - No effects on the ability to drive and use machines have been reported, and none are expected due to the homeopathic dilutions.
- Zeel® T ointment
  - Not applicable.

8 Use in clinical practice

Place in therapy

For patients
Zeel® T is used to effectively and safely manage the symptoms of osteoarthritis and rheumatic joint diseases of various etiologies. It has very few associated adverse effects (known allergy (hypersensitivity) to one or more of the ingredients), few contraindications (do not use during pregnancy and lactation) and no known drug interactions, and is suitable for acute and longer-term use.

In addition, the recent MOZArT study investigated patients with moderate-to-severe chronic knee osteoarthritis (OA) randomized to 3 weekly intra-articular co-administration of both Traumeel® and Zeel® T (n=119) or saline (n=111). The significant reduction in pain observed with Traumeel®/Zeel® T versus placebo could provide a safer alternative to the use of long-term NSAIDs for the relief of pain in this chronic condition.[1]

KEY FACT

Zeel® T is used to effectively and safely manage the symptoms of osteoarthritis and rheumatic joint diseases of various etiologies.

For healthcare professionals
Consider using Zeel® T formulations in:
- Patients who have osteoarthritis and rheumatic joint diseases of various aetiologies
- Patients with osteoarthritis and rheumatic joint diseases who have contraindications to conventional treatments
- Patients who have suffered from adverse effects from conventional treatments, especially in treatments extending over 10 days in the past or are not able to take conventional treatments
- Patients who are taking concurrent therapy for osteoarthritis and rheumatic joint diseases but not achieving adequate efficacy, including those with established disease

Formulations
Zeel® T is available in three formulations for flexibility of use and to maximize patient convenience and compliance. It can be obtained in:
- Ampoules for injection
- Ointment
- Oral tablets

The formulations contain the following number of active ingredients (see Section 3):

Zeel® T ampoules for injection	Zeel® T ointment	Zeel® T tablets
14	15	15

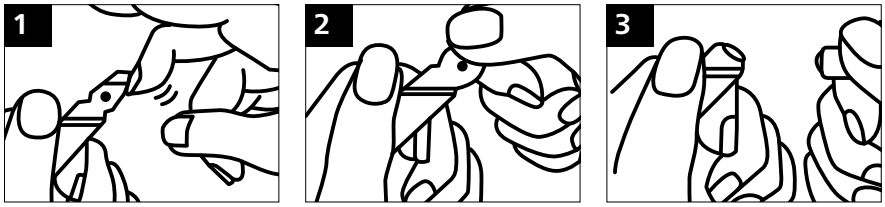
Medication names, indications and formulas may vary from country to country; package inserts provide country-specific information.

Dosing recommendations

Zeel® T ampoules for injection
Unless otherwise prescribed:
- Standard Dosage:
  - Adults: 1 ampoule 1 to 3× weekly.
- Acute or Initial Dosage:
  - Adults: 1 ampoule daily, and then continue with standard dosage.

Method of Administration: Zeel®, Solution for injection may be administered by the s.c., i.d., i.m., i.a. or i.v. route.

Instructions for opening glass vial (ampoule):



Cutting open the glass ampoule is not necessary. Hold the ampoule head up at an angle, and tap/shake down the solution contained in the ampoule head. Then break off the ampoule head by applying pressure away from the color dot.

Zeel® T ointment
Unless otherwise prescribed:
- Standard Dosage:
  - Adults: Apply 2 to 4× daily.

Method of Administration: For external use only. Apply a thin layer over the affected area.

Zeel® T tablets
Unless otherwise prescribed:
- Standard Dosage:
  - Adults: 1 tablet 3× daily.
- Acute or Initial Dosage:
  - Adults: 1 tablet every ½ to1 hr., up to 12× 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.

Pharmaceutical particulars

Storage
Store at room temperature. Protect from light.

Experience

Zeel® T has been researched for over 40 years, and has been used extensively by millions of patients in more than 30 countries worldwide.

9 Summary: the benefits of Zeel® T

- Scientifically demonstrated and clinically proven efficacy in osteoarthritis and rheumatic joint diseases.
- Multi-targeted mechanism of action mediated by its various ingredients that involves chronic inflammation, prevention of vascularization of the cartilage and endochondrium, remodeling and protection of cartilage, and alteration to cartilage mechanics.
- Intra-articular co-administration of Traumeel® and Zeel® T has been shown, in a large randomized controlled trial (MOZArT), to be an effective treatment for pain in OA of the knee and to improve physical function.
- Very rarely reported adverse effects, few contraindications and no known drug interactions.
- Very well-tolerated.
- Can be safely combined with natural or conventional treatments but is effective as monotherapy.
- Suitable for acute and longer-term treatment.
- High patient and physician satisfaction with therapy.

10 References

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11 Summary of product characteristics

Zeel® T formulations and dosing recommendations

Zeel® T: Tablets • Injection solution • Ointment

Compositions: ***Tablets:*** 1 tablet = 301.5 mg containing: Active ingredients: Acidum DL-alpha liponicum D6 0.03 mg, Acidum silicicum D6 3.00 mg, Arnica montana D1 0.60 mg, Cartilago suis D4 0.30 mg, Coenzym A D6 0.03 mg, Embryo totalis suis D4 0.30 mg, Funiculus umbilicalis suis D4 0.30 mg, Nadidum D6 0.03 mg, Natrium diethyloxalaceticum D6 0.03 mg, Placenta totalis suis D4 0.30 mg, Rhus toxicodendron D2 0.54 mg, Sanguinaria canadensis D3 0.45 mg, Solanum dulcamara D2 0.15 mg, Sulfur D6 0.54 mg, Symphytum officinale D8 0.15 mg. Excipients: Lactose monohydrate 296.94 mg, magnesium stearate 1.50 mg. ***Injection solution:*** 2.0 g containing: Active ingredients: Acidum DL-alpha liponicum D8 2.0 mg, Arnica montana D4 200.0 mg, Cartilago suis D6 2.0 mg, Coenzym A D8 2.0 mg, Embryo totalis suis D6 2.0 mg, Funiculus umbilicalis suis D6 2.0 mg, Nadidum D8 2.0 mg, Natrium diethyloxalaceticum D8 2.0 mg, Placenta totalis suis D6 2.0 mg, Rhus toxicodendron D2 10.0 mg, Sanguinaria canadensis D4 3.0 mg, Solanum dulcamara D3 10.0 mg, Sulfur D6 3.6 mg, Symphytum officinale D6 10.0 mg. Excipients: Sodium chloride 17.6 mg, water for injections 1747.4 mg. ***Ointment:*** 100 g containing: Active ingredients: Arnica montana D3 1.500 g; Calendula officinalis Ø, Hamamelis virginiana Ø, 0.450 g each; Chamomilla recutita Ø, Acidum DL-alpha liponicum D6 0.010 g, Acidum silicicum D6 1.000 g, Arnica montana D2 0.300 g, Cartilago suis D2 0.001 g, Coenzym A D6 0.010 g, Embryo totalis suis D2 0.001 g, Funiculus umbilicalis suis D2 0.001 g, Nadidum D6 0.010 g, Natrium diethyloxalaceticum D6 0.010 g, Placenta totalis suis D2 0.001 g, Rhus toxicodendron D2 0.270 g, Sanguinaria canadensis D2 0.225 g, Solanum dulcamara D2 0.075 g, Sulfur D6 0.270 g, Symphytum officinale D8 0.750 g. Excipients: Cetostearyl alcohol (type A), emulsifying 8.007 g; ethanol 96% (V/V) 9.565 g; paraffin, liquid 9.342 g; white soft paraffin 9.342 g; water, purified 60.810 g.

Indications: ***Tablets, injection solution, ointment:*** Arthrosis/osteoarthritis, and/or rheumatic joint diseases.

Contraindications: ***Tablets, injection solution, ointment:*** Known allergy (hypersensitivity) to one or more of the ingredients.

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

Side effects: ***Tablets, injection solution:*** Like all medicinal products, homeopathic medicines may cause side effects. In isolated cases transient skin allergies have been reported. The frequency of these effects is not known. ***Ointment:*** Like all medicinal products, homeopathic medicines can cause side effects in isolated cases, such as transient allergic reactions. The frequency of these effects is not known.

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

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

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

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

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

Package sizes: ***Tablets:*** Packs containing 50 and 250 tablets. ***Injection solution:*** Packs containing 10, 50 and 100 ampoules of 2.0 ml each. ***Ointment:*** Tubes containing 50 and 100 g.

Traumeel® formulations and dosing recommendations

Traumeel®: Tablets • Injection solution • Ointment • Gel

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

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

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

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

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

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

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

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

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

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

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

12 Disclaimer

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

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