Treatment with an Injectable Biological Preparation for Osteo-Arthrosis of the Knee: A Study Featuring 1845 Patients

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Key words: Zeel P injection solution, osteo-arthrosis of the knee, post-marketing drug survey.

Summary

This post-marketing drug survey was conducted with the objective of obtaining new knowledge on therapeutic administration of the antiarthrosis preparation Zeel P, as applied in medical practice. Admission to this study was granted only to patients who were suffering from arthrosis of the knee. Administration of Zeel P was exclusively by intraarticular injection. The period covered by this trial extended throughout four months, from September to December of 1992. A total of 190 orthopedists took part in this drug-monitoring study. These physicians treated 1845 patients with Zeel P and documented the results on standardized questionnaires: the collected data included case-history information, adjuvant medication, non-medicamentous adjuvant therapy, the scope of therapy provided, evaluation of the therapy, and tolerance to the medication. This post-marketing drug survey was designed as an accompanying study: i.e., during the progress of a series of injections, the physicians assessed at each therapeutic session knee stiffness and the degree of pain.

The following overall information was obtained:

1. On the average, each patient received intraarticular injection of one ampule of Zeel P, twice a week, over a period of 4-5 weeks.

2. The effectiveness of Zeel P injection solution was statistically apparent. Abatement of complaints was statistically verified after the first two injections. Pain upon initial knee movement, pain following exercise, continuous pain, and stiffness in the joint all decreased significantly in a linear manner during the course of treatment. This effectiveness was apparent throughout the entire scale of pain intensity: no pain, slight pain, moderate pain, and severe pain.

3. At the end of treatment, 93.1% of the patients assessed the therapy as positive: i.e., from satisfactory to very good.

4. The tolerance of Zeel P was good. The side-effect rate, referenced to the entire number of injections administered, was 0.45%. The only side effects actually registered were signs of local inflammation, which all abated.

1. Introduction

Following only cardiovascular disorders, rheumatic diseases rank second in frequency among all chronic illnesses in Europe [Bjelle, 1987]. Generally, the designation rheumatism is applied to all syndromes for which the only common characteristic is pain in the musculoskeletal system. Causative factors for the continuously increasing number of rheumatic illnesses may be found among the attributes of life practiced in industrialized countries: e.g., lack of exercise, loss of muscular strength, inappropriate diet, and overweight [Krebs, 1987]. It has been estimated that 12-25% of all patients who avail themselves of services provided by national health systems suffer from rheumatic disorders. As a result, this complex of symptoms represents one of the primary burdens borne by the health facilities of a country [Wagenhauser, 1984]. The national economic losses attributed to rheumatic disorders are therefore highly significant. In Germany, the treatment of all patients suffering from rheumatism alone requires several million trips to physicians, and an equivalent number of therapeutic applications. Each year in Germany, approximately 50 million man-days of work are lost because of rheumatic disorders, and the number of early retirees due to rheumatism rises continuously. Rheumatism has in fact become the most expensive disease in industrial countries [Krebs, 1987]. During 1992 in Germany, for example, physicians made diagnoses of arthrosis almost 17 million times, and prescribed medication for treatment of this indication around 20 million times.

In general, physicians administer antirheumatics in the form of non-steroidal antinflammatory drugs (NSAID) and chondroprotective medication. The antiarthrosis preparation Zeel P injection solution is a combination homeopathic medication, the formulation of which was developed on an empirical therapeutic basis. It is manufactured in accordance with the...
German Homeopathic Pharmacopoeia (HAB). The individual constituents contained in Zeel P make it effective in treatment of disorders which include osteo-arthritis of the knee, spondylarthrosis, polyarthrosis, and peri-arthritic humeroscapularis. The action of Zeel P injection solution is characterized by reliable effectiveness, and it satisfies requirements of patients for low-risk therapy [Hieber, 1971; Schlufter, 1975].

2. Methodology of the study
2.1 Conduct of the study
This post-marketing drug study was conducted with the objective of obtaining new knowledge on the therapeutic employment of the antiarthrosis preparation Zeel P. It was designed to gain data on the application, effectiveness, and tolerance under conditions of routine daily medical practice. The period of the study covered four months, from September to December of 1992. A total of 190 orthopedists took part in this survey. These physicians treated 1845 patients with Zeel P and documented the results on standardized questionnaires. Data were registered only for patients who were suffering from osteo-arthritis of the knee. Application of Zeel P injection solution was by intraarticular injection. Otherwise, there were no further restrictive criteria for including or excluding patients: i.e., conduct and extent of treatment were left absolutely to the discretion of the attending physicians (e.g., the number of injections and any additional therapy conditions). The drug-monitoring study was conducted on a prospective basis.

The attending physicians entered the following data on the questionnaire:
- Personal data on the patients: sex, age, weight, and height
- Cause and duration of the osteo-arthritis
- Previous therapy received by the patients (medicamentous or non-medicamentous).

Since the drug monitoring was designed to be conducted during the progress of therapy, the physicians were asked to rate the stiffness of the joint as well as pain upon initial knee movement, pain following exercise, and continuous pain during every treatment session: in each case, before the injection. The pain rating scale was as follows: no pain, slight pain, moderate pain, and severe pain. The physician also registered data on the following during each therapy session: adjuvant medication, non-medicamentous adjuvant therapy, the amount of Zeel P applied per injection, the employment of a local anesthetic, and the appearance of side effects. If side effects had appeared, the physician described them in detail on a separate report form. At completion of treatment, the therapist made a final overall evaluation of the results of the entire therapy. The following choices were possible:
- Very good = complete relief from symptoms
- Good = definite improvement
- Satisfactory = slight improvement
- Unsuccessful = no change
- Worsening.

2.2 Processing of data and statistical analysis
Although data were missing on various parameters in a few cases, it was possible to include all 1845 questionnaires in the analysis procedure. With the aid of a special statistics program, the data of each questionnaire were entered and subsequently analyzed by statistical techniques in order to reveal their interrelationships and their inner structure (by methods of inferential statistics for determination of significance). This drug-monitoring study investigated the effects of Zeel P treatment on the degree of severity of the four main clinical symptoms of osteo-arthritis of the knee (see above). Statistical investigation was made for samples taken from the following:

1. The entire population of 1845 patients
2. The subpopulation of 380 patients treated only with Zeel P (monotherapy).

Both the chronological axis (i.e., the number of therapy sessions), as well as the degree of severity of the symptoms (i.e., their intensity) were measured on an ordinal scale. Consequently, coefficients of contingency (the nominal technique) and of rank correlation were used for statistical analysis [Landis et al., 1978; Mantel and Haenszel, 1959; Mantel, 1963]. A procedure for nominal data (chi-square test) was used to investigate the contingency arising from therapeutic sessions and intensity of the symptoms. The rank correlation, i.e., the results of investigating whether a linear correlation existed between frequency of therapy and severity of the symptoms, was examined by means of a chi-square-distributed derivative from the Pearson correlation (the Mantel Haenszel chi-square test), and by regression analysis with the data gained during the course of treatment. The aid provided by this analysis includes a correlation coefficient r, which represents the relationship between two variables: in this study, the severity of pain or knee stiffness, and the frequency of therapy. The values of r can lie between -1 and +1. The closer the correlation coefficient lies to -1 (negative correlation) or to +1 (positive correlation), the more reliable the linear relationship between the two variables (when r = 0, there is no correlation).

The purpose of employing statistical analysis here for the data collected during the course of treatment was to answer the following questions:

1. Is the effectiveness of the medication statistically evident, and is there a difference in effectiveness between therapy for the entire population and for the monotherapy subpopulation?
2. How does the intensity of the examined symptoms change during the course of treatment: i.e., is there a correlation between frequency of therapy and severity of the symptoms?
3. Is Zeel P also effective in application for slight and moderate symptoms?
4. How many injections are required to bring about statistical improvement in the symptoms?

3. Results of the survey

3.1 Characterization of the patients

Personal data on the patients reveal that there were considerably more women (61.2%) who participated in the drug-monitoring study than men (38.4%). For 0.4%, the patient's sex was not indicated. As expected, a large share of the patients was over 50 years of age: 81% (see Table 1).

The most frequent cause of osteo-arthritis of the knee was indicated as attrition: e.g., as resulting from overweight, strenuous work, or sports. The following causes followed, but with much lower frequency (see Table 2):

- Endogenous disorders, e.g., from aging and metabolic disturbances
- Acquired joint deformations, for example, as a result of inflammatory joint diseases
- Congenital dysplastic conditions, e.g., from flat socket formation or subluxation
- Medial meniscus damage
- Meniscectomy
- Tibial plateau fracture
- Fracture of the patella
- Posttraumatic conditions
- Idiopathic causes.

Unilateral osteo-arthritis of the knee was determined for 830 of the patients (45.0%) and bilateral, for 1,011 (54.870). For 4 patients there was no data. For the bilateral cases, the physicians documented only the more severely afflicted knee. Data on duration of the disorder reveal that approx. 25% of the patients suffered from the symptoms for less than one year; approx. 45% between 1 and 5 years; and about 30% for, longer than five years. Around 40% reported that they were physically active at work; approx. 60% were not in this situation. One must consider here, however, that around 54% of the patients were older than 60, and that a large proportion of them were retired. No data were available on physical activity conducted in years prior to this study.

Of the 1845 patients covered by this drug-monitoring study, 1253 (67.90%) had undergone therapy for osteo-arthritis of the knee within the six months immediately prior to participation in the study. Most frequently, these patients had received non-steroidal antiinflammatory drugs, and a lesser number, the following: corticosteroids, chondroprotective medication, the antiarthritis preparation Zeel P (ampules), Zeel tablets, and Zeel T ointment. About 13% of the patients had undergone non-medicamentous therapy. The most frequent forms here were electrotherapy, kinesitherapy, some form of radiation, and cryo-therapy (see Table 3).

3.2 Formulation of Zeel 1? injection solution:

one ampule of Zeel P injection solution contains the following constituents:

Cartilago suis (extract, 1:10) 22.00 ng
Funiculus umbilicals suis (extract, 1:10) 22.00 ng
Embryo suis (extract, 1:10) 22.00 ng

Sodium oxalaceticum 0.22 ng
(~)-a-lipoic acid 0.22 ng
Sanguinaria (extract, 1:10) 22.00 ng
Amica (mother tincture) 0.22mg
Dulcamara (mother tincture) 22.00 µg
Symphytum (mother tincture) 22.0 µg
Sanguinaria (mother tincture) 33.00 µg
Sulfur (mother tincture) 39.60 µg
Nadid 0.22 ng
Coenzyme A 0.22 ng
Zeel P injection (ampules), Zeel tablets, and Zeel T ointment.

3.3 Adjuvant medication

Within the context of this drug monitoring, the participating physicians were fundamentally allowed and even encouraged to employ adjuvant medication on the basis solely of their own discretion. Of the 1845 patients here, 479 (26.0%) received concomitant medication, and 1352 (73.3%) received medicamentous monotherapy. For 14 patients, there were no data (see Table 4). The application of local anesthetic for alleviation of pain during intraarticular injection was not considered to be employment of adjuvant.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>1129 (61.2)</td>
</tr>
<tr>
<td>male</td>
<td>709 (38.4)</td>
</tr>
<tr>
<td>no data given</td>
<td>7 (0.4)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>up to 50 years</td>
<td>349 (18.9)</td>
</tr>
<tr>
<td>51-70 years</td>
<td>1030 (55.8)</td>
</tr>
<tr>
<td>&gt;70 years</td>
<td>465 (25.2)</td>
</tr>
<tr>
<td>no data given</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>up to 60 kg</td>
<td>276 (14.9)</td>
</tr>
<tr>
<td>61-80 kg</td>
<td>1141 (61.9)</td>
</tr>
<tr>
<td>&gt;80 kg</td>
<td>421 (22.8)</td>
</tr>
<tr>
<td>no data given</td>
<td>7 (0.4)</td>
</tr>
<tr>
<td>Height</td>
<td></td>
</tr>
<tr>
<td>up to 160 cm</td>
<td>420 (22.8)</td>
</tr>
<tr>
<td>161-180 cm</td>
<td>1317 (71.3)</td>
</tr>
<tr>
<td>&gt;180 cm</td>
<td>101 (5.5)</td>
</tr>
<tr>
<td>no data given</td>
<td>7 (0.4)</td>
</tr>
</tbody>
</table>

Table 1: Characterization of the patients (percent data in parentheses).

<table>
<thead>
<tr>
<th>Cause</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attrition</td>
<td>1277 (58.7)</td>
</tr>
<tr>
<td>Endogenous disorders</td>
<td>497 (22.8)</td>
</tr>
<tr>
<td>Congenital dysplast. cond.</td>
<td>110 (5.1)</td>
</tr>
<tr>
<td>Acquired joint deformation</td>
<td>218 (10.0)</td>
</tr>
<tr>
<td>Misc. causes</td>
<td>74 (4.4)</td>
</tr>
</tbody>
</table>

Table 2: The most frequent causes of osteo-arthritis of the knee (percent data in parentheses; for some patients there was more than one cause).
medication. Of the 479 patients with adjuvant medication, around half received non-steroidal antiinflammatory drugs (NSAID), and approx. 30% took Zeel in tablet or ointment forms (see Table 5). In general, the physicians administered the accompanying medication throughout the entire course of treatment. Local anesthetic (e.g., Lidocain or Mepivacain) was concomitantly administered to 1339 patients (72.6%). The therapists employed Zeel P injection solution alone, as monotherapy, in 20.6% of the cases (for 380 patients).

### Table 3: Number of patients who had undergone therapy for osteo-arthritis of the knee within the six months immediately prior to participation in the study (percent data in parentheses; some patients received more than one type of therapy; NSAID = non-steroidal antiinflammatory drugs).

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zeel P + adjuvant medication + local anesthetic</td>
<td>367 (19.9)</td>
</tr>
<tr>
<td>Zeel P + adjuvant medication</td>
<td>112 (6.1)</td>
</tr>
<tr>
<td>Zeel P + local anesthetic</td>
<td>972 (52.7)</td>
</tr>
<tr>
<td>Zeel P (medicamentous monotherapy)</td>
<td>380 (20.6)</td>
</tr>
<tr>
<td>No data recorded</td>
<td>14 (0.7)</td>
</tr>
</tbody>
</table>

### Table 4: Numerical compilation of the various treatment groups (percent data in parentheses)

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAID</td>
<td>272 (49.8)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>54 (9.9)</td>
</tr>
<tr>
<td>Chondroprotective medication</td>
<td>53 (9.7)</td>
</tr>
<tr>
<td>Zeel T ointment</td>
<td>93 (17.0)</td>
</tr>
<tr>
<td>Zeel tablets</td>
<td>74 (13.6)</td>
</tr>
</tbody>
</table>

3.4 Non-medicamentous adjuvant treatment

Non-medicamentous accompanying therapy was provided to 911 of the patients (49.4%); 930 received none (50.4%). No data was recorded for four patients. Electrotherapy was the most frequent non-medicamentous form, followed by cryotherapy and kinésithérapy. As a rule here as well, the therapists employed non-medicamentous accompanying therapy throughout the entire treatment phase (see Table 6).

### Table 5: Number of patients who received medicamentous adjuvant medication (percent data in parentheses; some patients received more than one type of therapy; NSAID = non-steroidal antiinflammatory drugs).

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAID</td>
<td>752 (37.0)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>300 (14.7)</td>
</tr>
<tr>
<td>Chondroprotective medication</td>
<td>270 (13.3)</td>
</tr>
<tr>
<td>Zeel P injection solution</td>
<td>221 (10.9)</td>
</tr>
<tr>
<td>Zeel T ointment</td>
<td>41 (2.0)</td>
</tr>
<tr>
<td>Zeel tablets</td>
<td>29 (1.4)</td>
</tr>
<tr>
<td>Knee surgery</td>
<td>153 (7.5)</td>
</tr>
<tr>
<td>Non-medic, treatment</td>
<td>269 (13.2)</td>
</tr>
</tbody>
</table>

3.5 Data on number of therapeutic measures

Within the context of this injection series, the participating therapists carried out a total of 17,159 outpatient therapeutic measures. Calculations on the basis of this data reveal an average treatment frequency of 9.3 therapeutic measures per patient (for 81% of all patients). On the basis of two treatment measures per week, this amounts to an average duration of treatment of 4-5 weeks per patient. All patients taken together received a total of 16,974 injections (for an average of 9.2 injections per patient), with overall consumption of 19,742 Zeel P ampules. This amounts to an average of 10.7 ampules per patient. The physicians therefore generally injected one ampule per application; only in exceptional cases did they inject two ampules at one time.

3.6 Monitoring during therapy

The physicians were asked to rate knee stiffness, as well as pain upon initial knee movement, pain following exercise, and continuous pain, during every treatment session: in each case, before the injection. In this manner, effectiveness of treatment was continuously monitored. The ratings before the first injection were used as basis values for the individual parameters. Figs. 1 - 4 graphically represent the results of the regression analysis performed on all data collected during the course of therapy. One of the primary clinical symptoms of osteo-arthritis of the knee is stiffness, combined with a feeling of tension, after relatively long periods of inactivity. At the beginning of treatment, 12.0% of the patients (basis value) complained of severe knee stiffness. At the end of treatment, this figure was only 1.6% (a decrease of 87%). Before the initial injection, 25% of the patients experienced no knee stiffness. After conclusion of therapy, this number had more than doubled: to 54%. The plot of the figures in Fig. 1 emphasizes this result. Knee stiffness decreased significantly in a linear manner along with the progress of treatment.
Table 6: Number of patients who received non-medicamentous adjuvant therapy (some patients received more than one form; percent figures in parentheses).

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Patients</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrotherapy</td>
<td>605</td>
<td>(44.3)</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>270</td>
<td>(19.8)</td>
</tr>
<tr>
<td>Kinesitherapy</td>
<td>269</td>
<td>(19.7)</td>
</tr>
<tr>
<td>Balneotherapy</td>
<td>91</td>
<td>(6.7)</td>
</tr>
<tr>
<td>Massage</td>
<td>21</td>
<td>(1.5)</td>
</tr>
<tr>
<td>Misc. Therapy</td>
<td>109</td>
<td>(8.0)</td>
</tr>
</tbody>
</table>

Similar results were obtained for pain with onset of movement, which usually occurs upon initial exercise after a relatively long period of inactivity. At the beginning of monitoring, approx. 24% of the patients indicated severe pain upon onset of movement. After conclusion of treatment, this was only 1.10%, for a decrease of 95%. In conjunction with this development, the number of patients without such movement-onset pain increased from 6% to around 42%. In other words, there is also a linear relationship between the severity of movement-onset pain and the frequency of application (see Fig. 2).

Pain following exercise (i.e., a dull pain after relatively long application of loads) also declined significantly in a linear manner. At the beginning of treatment, 33% of the patients reported experiencing severe pain after exercise (i.e., a dull pain after relatively long application of loads) also declined significantly in a linear manner. At the beginning of treatment, 33% of the patients reported experiencing severe pain after exercise, which usually occurs upon initial exercise after a relatively long period of inactivity. After the end of therapy, this proportion had decreased by 92%. During the same period of time, the number of patients who experienced no pain after exercise increased from 0.80% to 28.7% (see Fig. 3).

The analysis of the ratings for continuous pain provides a result which is fundamentally the same as for the two other types of pain. The number of patients with severe continuous pain decreased by 93% during the course of treatment, and the number of patients without continuous pain tripled, to a level of 67.1%. These parameters likewise demonstrate a linear relationship between severity of pain and frequency of treatment (see Fig. 4).

**3.7 Monotherapy with Zeel P injection solution**

As stated earlier, 26% of the patients received adjuvant therapy. Of these, the primary form of therapy for approx. 50% of the adjuvant-therapy cases consisted of administration of non-steroidal antiinflammatory drugs (NSAID). If the analysis also includes local anesthetics, about 79% of all patients received some medication in addition to Zeel P injection solution. Monotherapy, i.e., treatment exclusively with Zeel P injection solution, was administered to 20.6% of the patients (380) who took part in the postmarketing drug survey. Additional, separate evaluation consequently took place for this group. The average treatment frequency and the total number of ampules per patient were not strikingly different from the corresponding figures for the overall study population. Figs. 1-4 also represent the evaluation of data on changes observed in knee stiffness and in the various types of knee pain among the Zeel P monotherapy subpopulation. In this group as well, the number of patients who experienced severe knee stiffness decreased significantly during the course of treatment (a decrease of 90.5%). Simultaneously, the number of patients without knee stiffness increased by 65% (see Fig. 1). The frequency of severe pain with onset of movement also decreased during treatment in a linear manner. Whereas approx. 17% indicated severe movement-onset pain at the beginning of therapy, the figure was only 0.5% at the end of treatment: a reduction of 97%. In parallel with this development, the proportion of patients without movement-onset pain quintupled (see Fig. 2). In the monotherapy group, severe pain following exercise decreased by 92%. During the same period of time, the number of patients without exercise-induced pain increased twenty-fold (see Fig. 3). Intraarticular injection of Zeel P likewise significantly reduced severe continuous pain: by 90%. The number of persons free from severe continuous pain had doubled by completion of therapy (see Fig. 4).

Fig. 5 once again summarizes the frequency of freedom from the individual clinical symptoms recorded at the beginning of treatment (basis val-
1. The effect of treatment was virtually the same in both groups.

2. The frequency of freedom from symptoms increased in a linear manner during the course of treatment.

3. Rating of the less severe symptoms demonstrated a reciprocally quadratic progression.

4. There was a linear decrease in the ratings for moderate symptoms.

5. The decrease in severity of the more serious symptoms was virtually exponential in nature.

In the area of slight to moderate symptom severity, the recorded data indicate a linear influence of Zeel P treatment toward achieving an alleviation of these symptoms. The explorative question concerning the critical quantity of the medication was answered by successive analysis of the data from the first compared to the following data-acquisition point (i.e., the examinations immediately prior to injection). Statistically significant effects became apparent after only the second injection. The minimum requirement for statistically significant improvement amounted to more than two injections for the patients who received only Zeel - P (monotherapy), and/or for treatment of knee stiffness, and/or for symptoms of slight to moderate intensity.

3.8 Results of therapy

At the end of therapy, the participating physicians performed a concluding, overall rating of the therapy. Evaluation of these ratings showed that treatment achieved definite relief for the symptoms of approx. 53% of the patients, and complete freedom from complaints for every fifth patient. The

Biological Therapy / Vol. XIII/ No. 11995
Knee stiffness

Pain with onset of movement

Pain following exercise

Continuous pain

In percent

- Basis value
- After 10 treatment sessions

Fig. 5: Proportion of the patients (in percent) who were free of pain at the beginning of the study (basis values), and after ten treatment sessions with Zeel P injection solution.

Treatment was completely unsuccessful for only 6.2% of the patients. The therapists diagnosed worsening for merely 0.6% of the patients. On the whole, findings revealed that 93.1% of all patients achieved a positive treatment result. The therapy results of the monotherapy group are comparable to those of the entire study population. Here as well, approximately half of the patients enjoyed good results. The number of monotherapy patients with very good outcome of therapy was even five percent points greater than that of the overall population. On the whole, 91.970 of the monotherapy patients achieved positive results of therapy (see Fig. 6).

3.9 Tolerance

If side effects were diagnosed during the treatment sessions, the physicians described them on a special report form. Side effects appeared for 69 patients. Based on the entire number of injections administered (16,974), this amounts to a side-effects quota of 0.45%. In all cases, the side effects consisted of local inflammation. The most frequent specific form of side effects was effusion into a joint cavity: 44 cases (some patients suffered from more than one type of side effect). In terms of the five cardinal symptoms of inflammation according to classical medicine, the therapists diagnosed dolor (physical pain) in 41 cases, calor (excessive bodily heat) in 22 cases, and rubor (redness of the skin) in 9 cases. Joint swelling without effusion appeared only with one patient. All the documented side effects were reversible: i.e., permanent damage occurred in no cases. Treatment of the side effects was unnecessary in 24 cases. In 15 cases, conservative treatment sufficed (e.g., ice packs). The physicians applied medication for side effects with 29 patients: e.g., Diclofenac, Ibuprofen, or Dexamethason. Puncture of the joint effusion was conducted for 36 patients. Of the 69 patients with side effects, 35 of them prematurely terminated their treatment of osteo-arthritis of the knee with Zeel P. Of these 35, 25 indicated the side effects as the reason for their stopping the therapy with Zeel P. Two patients stopped because of lack of therapeutic effectiveness, one patient had to enter the hospital for inpatient treatment, and one patient had to travel abroad for a lengthy period of time.

With respect to the frequency of side effects, there was no noteworthy difference between the monotherapy group and the entire study population: 0.45% for the overall group, and 0.46% for the monotherapy patients (the percent indication is based on the total number of injections administered). Six persons in the monotherapy prematurely terminated their treatment: in all cases, local inflammation was the cause (see above).

4. Interpretation of Results

Degenerative disorders of large and small joints are among the most commonly encountered chronic disorders in everyday medical practice. The ge-
neric term *arthrosis* is primarily used to cover all non-inflammatory, degenerative structural damage suffered in the area of the *articular* cartilage, the bordering bone, and the *articular* capsule. Osteo-arthritis of the knee, one of the most common forms of arthrosis, is caused by metabolic anomalies, neuropathic and posttraumatic alterations, blood-circulation disorders in *articular* cartilage, and disorders in the equilibrium between the loads applied to *articular* cartilage and its ability to sustain such burdens.

Therapy with *Zeel P* injection solution is based on the concept of restoring normal physiological conditions in a diseased joint. This is achieved by promoting anabolic processes with simultaneous retardation of catabolic functions. The objective of the post-marketing drug survey conducted here was the obtaining of new knowledge on the application, effectiveness, and tolerance of *Zeel P* injection solution under the conditions of daily medical practice.

A total of 1845 persons with osteo-arthritis of the knee took part in this study. The distribution of ages (81% of these patients were older than 50) and of sex (61.2% were female) within the total study population corroborates earlier-gained evidence: i.e., that it is especially older persons, primarily women, who suffer from arthritic complaints. The nature of this disorder itself explains this phenomenon. An essential factor in the development of osteo-arthritis of the knee is age-related cartilage degeneration, since all bradytrophic tissues, not least because of their lack of vascular supply networks, are subject to regressive aging processes, accompanied by progressive loss of elasticity. Women are particularly affected by these processes, because the effects of age-related hormonal alterations also include metabolic disorders. The causative factors stated for osteo-arthritis of the knee are also typical for metabolic irregularities. For approximately 82% of the patients in this study, the physicians indicated attrition damages or endogenous disorders as causes. As a result, it maybe determined that the persons taking part in this drug-monitoring study constitute a representative cross-section with respect to age and sex distribution, as well as etiology.

Documentation performed parallel to therapy revealed the following average data: that the patients typically received two injections per week, each consisting of one ampule, over a period of 4 to 5 weeks. These results on application frequency and duration accord with experience gained earlier with *Zeel P* injection solution. The results obtained on effectiveness also corroborate experience gained over many years with *Zeel P* injection solution. For characterization of effectiveness, the participating physicians rated the severity of the four most important clinical symptoms of osteo-arthritis of the knee: pain upon initial knee movement, pain following exercise, continuous pain, and stiffness in the joint. Study results revealed that the number of persons with severe symptoms decreased on the average by 90%, and that the number of patients without complaints simultaneously and significantly increased during the course of therapy. In other words, there is a direct (linear) relationship between the abatement in symptoms and the frequency of medication application. There was no statistical difference in this respect between patients with adjuvant medication and those who were treated exclusively with *Zeel P* injection solution (monotherapy). This signifies that therapeutic superiority of combination medicamentous therapy is not apparent.

The data obtained on the *tolerance* of *Zeel P* injection solution corroborate the experience earlier gained that this combination preparation is well tolerated by patients. The side effects recorded were, without exception, cases of local inflammation which all abated. In no case did a patient suffer from systemic side effects such as those which commonly occur in this context in the gastrointestinal system. In treatment of osteo-arthritis of the knee with antirheumatics, it is precisely the gastrointestinal system which is frequently (in approx. 15% of patients) afflicted with side effects. These include the development of petechiae, erosion, as well as ulceration of the duodenum and the stomach: anomalies which often require supplementary medicamentous treatment.

According to Karch and Lasagna (1975), adverse side effects are involved once it is determined that the therapeutic agent has elicited an undesired harmful effect when administered in a dose which is customary for the *therapy* i.e., if it is possible to establish a *causal* relationship between the therapeutic agent and the adverse side effect. An adverse effect initiated by the failure of a specific therapy, or by the mode of application per se, is not considered an undesired side effect. If one investigates in detail the occurrence of the side effects observed in this *Zeel P* post-marketing drug survey, it may be seen that of the 69 patients suffering from a side effect 50 were administered a local anesthetic in conjunction with *Zeel P*. The probability of side effects therefore increased in this study upon application of local anesthetic. For these 50 patients with simultaneous administration of a local anesthetic, therefore, a causal connection between the side effects suffered and administration of *Zeel P* injection solution cannot be established with conclusive certainty. The remaining 19 patients received no additional local injections in addition to *Zeel P*. If these circumstances are considered, then the side-effects rate, with reference to total injections, falls to 0.11%. Due to the individual needs of the patient, however, it is frequently essential to employ local anesthetic in conjunction with *intraarticular* injections. The question therefore arises as to what extent the side effect results from the mode of application, and whether the injected medication itself is actually not responsible at all. According to studies conducted by Bernau et al. (1985), it is practically impossible, even if a physician uses the thinnest injection cannulae, to avoid injecting into joint cavities the plugs of skin punched out when a hypodermic
needle pierces the skin. It is possible that these skin cells (e.g., keratinocytes) elicited the inflammation reactions observed in this study, as a result of production of interleukin 1 (IL 1) [Dowd et al., 1988]. The local inflammation symptoms can, however, also spontaneously develop occasionally because of the arthrosis-related conditions of irritation / inflammation existing in the knee joint. In such cases, they would not necessarily represent a direct consequence of the injection of medication. Upon consideration of all these potential factors capable of eliciting side effects, a causal relationship between Zeel P injections and the observed side effects is questionable. This statement is further supported by the following fact: 35 of the 69 patients with side effects prematurely terminated their treatment for gonarthrosis. The remaining 34 patients, on the other hand, continued their treatment with Zeel P and despite the occurrence of side effects achieved positive therapeutic results. The continued application of Zeel P, i.e., after the initial observance of side effects, induced repeated side effects in only eight cases. Here, it was not certain whether new side effects were involved, or whether the old side effects had not yet fully subsided. If one prepares a risk-benefit analysis on the basis of consideration of all these factors, one may conclude that the benefits of Zeel P treatment are definitely greater for the patient than is the risk involved.

The results from this post-marketing drug survey corroborate the previous experience which had been gained with this combination preparation, and which has been described in medical literature. Hieber [1971] and Kasanmascheff [1971] treated 107 and 101 patients, respectively, with Zeel P injection solution for gonarthrosis. They administered a total of 828 and 631 intraarticular injections, respectively, and achieved a therapeutic success rate of 93.6% and 88.07%, respectively. Schluter [1975] treated 90 patients for severe osteo-arthritis of the knee with 553 intraarticular injections of Zeel P injection solution, and achieved a success quota of 85.5°/0. In 1991 Potrafki and Steinbach reported on the treatment of 55 patients with Zeel P injection solution for rheumatic disorders (arthrosis and vertebral syndromes of the cervical spine, thoracic vertebral column, and lumbar spine) which resulted in significant relief of pain and enhancement of articular functioning for approx. 82% of the patients. These authors reported no side effects of local or systemic nature.

Finally, it may therefore be concluded that the therapeutic application of Zeel P injection solution is indicated for the treatment of osteo-arthritis of the knee. Of the patients participating in the post-marketing drug survey, 93.1% positively assessed the overall therapy. This post-marketing study therefore verifies the effectiveness of Zeel P injection solution, the effectual formulation of this combination homoeopathic preparation, as well as its good toleration by the patients.

References


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Editor's Note:

The term osteo-arthritis, as used in this study, refers to a condition characterized by non-inflammatory, degenerative structural damage in the area of articular cartilage, bordering bone, and the articular capsule. The route of administration featured in this study, intra-articular injection, is frequently practiced in Europe. The manufacturer of Zeel, Biologische Heilmittel Heel GmbH, does not promote this type of injection in the U.S., due to the intricacy the procedure requires. Heel will assume no liability resulting from complications resulting from improper intra-articular injection of any Heel preparation.

The product Zeel is available in the United States from BHI in the dosage forms of oral vials, tablets, and ointment.