

EMS SWISS DOLORCLAST®

SUMMARY OF CLINICAL STUDY RESULTS FDA / PMA APPROVAL

TREATMENT OF PAINFUL HEEL

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GENERAL INFORMATION

Device Generic Name: Orthopedic Extracorporeal Shock Wave Therapy Device

Device Trade Name: EMS Swiss DolorClast®

Applicant Name and Address: EMS Electro Medical Systems S.A.
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INTRODUCTION

The EMS Swiss DolorClast® is an extracorporeal shock wave device intended for use in applying shock waves to the heel of patients who have chronic proximal plantar fasciitis and who have failed prior conservative therapies. The EMS Swiss DolorClast® is intended to be used by medical professionals who have been trained in its operation.

CLINICAL STUDY

A multi-center, randomized, placebo-controlled, prospective, double-blind clinical study was conducted with two groups: a group receiving ESWT with the EMS Swiss DolorClast® and a control group receiving a sham treatment. Patients were treated at eight clinical sites. For the purpose of this study, chronic proximal plantar fasciitis was defined as painful tenderness localized at the inferomedial aspect of the calcaneal tuberosity close to the insertion area of the plantar fascia that had persisted for at least six months prior to study enrollment.

SUBJECT ELIGIBILITY

The eligibility criteria described in the study protocol were as follows:

INCLUSION CRITERIA

All of the following criteria have to be met for inclusion of a subject into the study:

1. Age above 18 years
2. Ability of subject or legal respondent to give written informed consent after being told of the potential benefits and risks of participating in the study;
3. Signed informed consent
4. Diagnosis of painful heel syndrome (i.e., chronic proximal plantar fasciitis) proven by clinical examination;
5. 6 months of unsuccessful conservative treatment i.e., must have undergone at least 2 unsuccessful non-pharmacological treatments and at least 2 unsuccessful pharmacological treatments.
6. Time gap of at least:
 - 6 weeks since the last cortisone injection
 - 4 weeks since the last iontophoresis, ultrasound and electromyostimulation
 - 1 week since the last NSAIDs and
 - 2 days since the last analgesics, heat, ice, massage, stretching, night splinting and orthosis
7. Scores of ≥ 5 on both VAS pain scales (heel pain when taking first steps of the day and heel pain while doing daily activities);
8. Willingness to refrain from the following painful heel related, concomitant therapies: iontophoresis; electromyostimulation; ultrasound; NSAIDs; steroid injections or surgery – Until visit of this study (shoe modifications and surgery rescue pain medication are allowed during the entire study);
9. Willingness to keep allowed a subject heel pain medication and other heel pain therapy diary until 12 months after the last treatment;

10. Females of child bearing potential may be entered if they provide negative urine pregnancy test before the first ESWT treatment;
11. Willingness of females of childbearing potential to use contraceptive measures for 2 months after enrollment into the study.

EXCLUSION CRITERIA

Any of the following excludes a subject from the study:

1. Subjects suffering from tendon rupture, neurological or vascular insufficiencies of the painful heel;
2. Inflammation of the lower and upper ankle;
3. History of rheumatic diseases, and/or collagenosis and/or metabolic disorders;
4. Subjects with a history of hyperthyroidism;
5. Malignant disease with or without metastases;
6. Subjects suffering from Paget disease or calcaneal fat pad atrophy;
7. Subjects suffering from osteomyelitis (acute, sub acute, chronic);
8. Subjects suffering from fracture of the calcaneus;
9. Subjects with an immunosuppressive therapy;
10. Subjects with a long-term treatment with corticosteroid;
11. Subjects suffering from diabetes mellitus, severe cardiac or respiratory disease;
12. Subjects suffering from coagulation disturbance and/or therapy with Phenprocoumon, Acetylsalicylic acid or Warfarin;
13. Bilateral painful heel, if both feet need medical treatment;
14. Subjects who, at entry, are known to have treatment planned within the next 8 weeks, which may abruptly alter the degree or nature of pain experienced such that extracorporeal shock wave therapy will no longer be necessary (e.g., surgery);
15. Time gap of less than:
 - 6 weeks since the last cortisone injection;
 - 4 weeks since the last iontophoresis, ultrasound and electromyostimulation;
 - 1 week since the last NSAIDs and 2 days since the last analgesics, heat, ice, massage, stretching, night splinting and orthosis;
16. Previous surgery of the painful heel syndrome;
17. Previous unsuccessful treatment of the painful heel with a similar shock wave device;
18. History of allergy or hypersensitivity to bupivacaine or local anesthetic sprays;
19. Subjects with significant abnormalities in hepatic function;
20. Subjects in a poor physical condition;
21. Pregnant female;
22. Infection in the treatment area recently or in medical history;
23. History or documented evidence of peripheral neuropathy such as nerve entrapment, tarsal tunnel syndrome, etc.;
24. History or documented evidence of systemic inflammatory disease such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, aseptic bone necrosis, Reiter's syndrome, etc.;
25. History or documented evidence of worker's compensation or litigation;
26. Participation in an investigational device study within 30 days prior to selection, or current inclusion in any other clinical study or research project;
27. Subjects who, in the opinion of the investigator, will be inappropriate for inclusion into this clinical study or will not comply with the requirements of the study.

STUDY DESIGN

Subjects who signed the study informed consent form and met the study eligibility criteria were randomized to receive either the active or placebo device treatment in a 1:1 allocation. The placebo handpiece and applicator were constructed so that the pressure impulse was blocked from being transferred to the treatment site, but otherwise was the same as the active handpiece and applicator. After a screening visit to determine eligibility (Visit 1), the study started at Visit 2 with the first treatment. The treatment protocol was the same for active and placebo subjects. The protocol specified a total of 2500 active impulses at each of three visits, spaced 2 weeks apart. The first 500 shocks were applied at gradually increasing pressure (from 2 to 4 bar) in order to desensitize the patient to the pain of the impulses. The treatment impulses were applied at a pressure of 4 bar. If the patient could not tolerate the treatment pain during the introduction phase, the investigator was allowed to perform a local anesthesia in these subjects using 5-10 ml of 0.5% bupivacaine in a medial application or a local anesthetic spray. The follow-up period began 1 week after the last treatment. Follow-up evaluations were performed by study investigators who were not involved in the subject's treatment and were blinded as to the subject's randomization. Follow-up visits continued at 6 and 12 weeks following the last treatment (16 weeks after randomization). Patients who had sufficient pain relief to meet the study definition of "responders" continued in the study at this point and were followed again at 6 and 12 months after last treatment. The success rate was defined with at least 60 percent reduction in pain when taking first steps in the morning and while doing daily activities or if the subject was satisfied with the outcome of the treatment, was able to work (if applicable) and did not require concomitant therapy to control heel pain.

STUDY POPULATION

A total of 251 subjects formed the safety population for the study: The patients were enrolled in five German centers and in three US centers. 129 were randomized to the active group and 122 to placebo. 97% of this patient population (243/251) received at least one treatment and had at least one follow-up evaluation. Of these 243 patients, 125 were in the ESWT group and 118 were in the placebo group. 87% of the safety population had all three treatments and completed all follow-up visits through Visit 7 (per Protocol Population, PP). Of the 219 Per Protocol patients, 111 were in the ESWT group and 108 were in the placebo group. Analysis of the subject baseline characteristics and demographic data for the ITT (Intend To Treat) patient population demonstrate that the ESWT and placebo groups were well comparable at baseline on all variables and all p-values were statistically not significant ($p > 0.1$).

PRECAUTIONS

Patient pain tolerance is enhanced by starting at a low pressure and gradually increasing the pressure up to 4 bar over. The treatment energy level has to be achieved after 500 impulses. However, if the patient is not able to tolerate the treatment, then local anesthesia should be administered. Patients who are unable to tolerate local or regional anesthetic or cannot tolerate the treatment pain even with a

local or regional anesthetic should not be treated with this device and should consider alternative therapies. All but one patient treated in the EMS Swiss DolorClast® clinical study were able to tolerate the treatment without anesthesia. Although no patients in the clinical study experienced a vaso-vagal reaction during treatment, this reaction has been reported with other types of extracorporeal shock wave therapy. If this reaction occurs, the treatment should be interrupted and the patient reclined to a supine position until symptoms disappear. The housing of the EMS Swiss DolorClast® is not watertight. The handpiece is neither watertight nor autoclavable and should not be immersed into liquids nor chemically disinfectants.

The safety and effectiveness of the EMS Swiss DolorClast® to treat painful heel has not been established for patients with the following conditions:

- Under 18 years of age
- Diseases or disorders of the nerves in the foot to be treated
- Infection in the area to be treated
- Current or recent therapy that would compromise tissue healing
- Problems with circulation or bleeding
- History or documented evidence of immune system deficiencies (autoimmune disease)
- Significant disease of the blood vessels in the foot to be treated
- Rheumatoid arthritis (pain, stiffness or swelling of the joints)
- Malignant disease with or without metastases in the heel
- Previous treatment of the painful heel with corticosteroid injections within 6 weeks of the EMS Swiss DolorClast® treatment or previous treatment with non-steroidal anti-inflammatory drugs within 1 week of the EMS Swiss DolorClast® treatment
- Previous surgery for painful heel
- Pregnant females

ADVERSE EVENTS

During the EMS Swiss DolorClast® clinical study, a total of 73 non-serious adverse events were reported during the 12 week follow-up period in 41 of the 129 patients (31.8%) receiving active treatment. Of these reports, 23 adverse events in 16 patients were considered to be not device related and 50 adverse events in 33 patients were considered to be device related. Eight patients reported both, device related and non-device related adverse events. In the placebo group, a total of 36 adverse events were reported in 27 of the 122 patients (22.1%) during the 12-week follow-up period. Of these reports, 25 adverse events in 19 patients were considered to be not device related, and 11 adverse events in 10 patients were considered to be device related. Two of these patients reported both device related and non-device related adverse events. Table 1 summarizes the adverse events that were considered to be related to the device. The most common adverse event associated with use of the EMS Swiss DolorClast® is pain or discomfort during treatment. This side-effect was noted by 23% of the patients treated with the EMS Swiss DolorClast® in the clinical study, but all patients except for one were able to complete their treatments without any anesthesia. In the majority of cases the duration of treatment pain was reported to be a maximum of less than 10 minutes.

Table 1: Summary of Device Related Adverse Events, Safety Population (n=251) at 12-week follow-up

Event	ESWT Group (N=129)			Placebo Group (N=122)		
	Events	Subjects	% Total Subjects	Events	Subjects	% Total Subjects
Pain or discomfort during treatment	43	30 ¹	23.26%	5	5	4.10%
Pain post-treatment	5	5 ²	3.88%	3	3	2.46%
Skin reddening	1	1 ³	0.78%	1	1	0.82%
Swelling and pain post-treatment	1	1	0.78%	1	1	0.82%
Numbness post-treatment	0	0	0%	1	1	0.82%

¹ Twenty subjects with pain during one treatment session, seven during two sessions, and three during three sessions

² Three subjects also reported pain during treatment.

³ This subject also reported pain during treatment.

TREATMENT INFORMATION

The majority of subjects in the safety population completed all three treatment sessions 90.7% (117/129) ESWT and 95.9% (117/122) placebo. The average number of impulses delivered per treatment session ranged between 2413 and 2451 and was very similar between the two treatment groups (p-value >0.5 for all treatment sessions). Placebo impulses were blocked from reaching the treatment area. Although 30 ESWT and 5 placebo subjects complained of pain during treatment, only one subject requested local anesthesia for the pain. Only one device malfunction was reported during the study (placebo applicator did not function and treatment was conducted with a second applicator). No subject in either group experienced an adverse event as a result of a device malfunction. The primary efficacy criteria was a composite of three measures of chronic proximal plantar fasciitis, evaluated using a 10 cm Visual Analog Scale (VAS): heel pain upon taking first steps of the day, heel pain while doing daily activities, and heel pain after application of the Dolormeter (a standardized pressure device). The composite result was calculated two ways. First on a continuous scale as the sum score of the three measurements and second on a binary scale (success/failure) with success being defined as greater than 60% reduction in VAS score compared to baseline 12 weeks after the last ESWT treatment on at least two of the three heel pain measurements. The primary time point for evaluating the efficacy of the treatments was 12 weeks following the third treatment session. Missing data was handled using the Last Value Carried Forward (LVCF) approach. Pain scores were adjusted for subjects who took interfering analgesics or had other therapies for their painful heel within predefined timeframes prior to evaluation visits by adding two points to their VAS scores for the affected visit.

Primary Efficacy Results

The primary efficacy results for the ITT (Intent To Treat) population demonstrate that the mean composite pain score for the ESWT group (sum of VAS scores for the three pain measures) decreased from 22.0 ± 3.24 at baseline to 9.7 ± 8.56 at Visit 7,

for a mean percent decrease (i.e., improvement) of 56%. In the placebo group, the mean composite pain score decreased from 21.6 ± 3.22 at baseline to 12.3 ± 9.39 at Visit 7, for a mean percentage decrease of 44%. These results show a statistically significant improvement in the mean composite VAS score for the ESWT group as compared to the placebo group (p=0.022, more than a small superiority on the Mann-Whitney estimator). The result for overall success rate, defined as greater than a 60% reduction in VAS pain scores on at least two of the three pain measures, was also statistically superior for the ESWT group as compared to placebo. 61% (75/123) of the ESWT subjects met this success criterion as compared to 42% (49/116) of the placebo subjects group (p=0.002, more than a small superiority on the Mann-Whitney estimator). The results for the Per Protocol population further support the efficacy of ESWT with the EMS Swiss DolorClast®. In this population, where all subjects received the full prescribed three treatments, the results for the ESWT group improved (as compared to the ITT population) while the results for the placebo group stayed essentially the same (as compared to the ITT population). The superiority of the Per Protocol ESWT group as compared to the Per Protocol placebo group is confirmed by this analysis (p<0.01 on both composite VAS score and overall success).

Secondary Efficacy Results

The secondary efficacy criteria included the Roles and Maudsley Score, SF-36 Quality of Life evaluation, investigator's global judgment of effectiveness, subject's satisfaction with their therapy outcome, and whether the subjects would recommend the EMS Swiss DolorClast® therapy to a friend. The ESWT group demonstrated statistically greater improvements from baseline to the primary endpoint 12 weeks after last treatment on all secondary measures as compared to the placebo group (P < 0.025 one-sided), and all effect sizes (Mann-Whitney) denote more than small superiority of the ESWT group.

LONG TERM OUTCOME: FOLLOW-UP RESULTS AT 6-MONTHS AND 12-MONTHS

Treatment responders at the primary end point stayed in the study and returned for two additional follow-up visits (6 months and 12 months following the last treatment). The evaluation procedures were the same in all visits. Subject diaries for responders were collected at the 12 month visit. The results 6 and 12-month after ESWTs were similar to the results described above. Results include the composite scores and overall success rate in accordance with the same criteria used for the primary efficacy results at the primary study endpoint. Missing data was handled using the Last Value Carried Forward (LVCF) approach. Pain scores were adjusted for subjects who took interfering analgesics or had other therapies for chronic proximal plantar fasciitis within predefined timeframes prior to evaluation visits by adding 2 points to their VAS scores for the affected visit. In both the EMS Swiss DolorClast® ESWT

group and the placebo group, the mean composite scores increased slightly from the scores at Visit 7. The results continue to show an improvement in the mean composite VAS score for the ESWT group as compared to the placebo group. Likewise, the overall success rate (defined as greater than 60 percent reduction in VAS pain scores on at least two of the three pain measures) for the ESWT group continued to be superior to that of the placebo group. These results confirmed that the results obtained at the 3-month primary efficacy end-point are maintained over a period of up to 12 months. Only six additional adverse events in five patients were reported during the 6-month and 12-month follow-up period (one patient in the ESWT group and four patients in the placebo group). None of these reported adverse events were considered to be related to the device.

CONCLUSIONS

The results of the clinical study provide reasonable assurance that the EMS Swiss DolorClast® is safe and effective when used in accordance with the device labeling. The results of the multi-center, randomized, placebo-controlled, double-blinded clinical study demonstrate that treatment with the EMS Swiss DolorClast® provides significant pain-relief to patients with symptoms of proximal plantar fasciitis of at least 6 months duration who had failed previous conservative therapy.

TREATMENT OF CHRONIC PROXIMAL PLANTAR FASCIITIS



1. The treatment site is located using palpation and patient feedback regarding the area of pain.



2. After locating the treatment site, the skin of the treatment area is marked.



3. Use EMS Swiss DolorClast® coupling gel for improved coupling.



4. Gently rub the applicator tip over the site of treatment in multiple impulse mode. Exert as much pressure as the patient can reasonably tolerate (use the Ø15 mm applicator).

GENERAL RECOMMENDATION

Local anesthesia, if necessary, should be applied by subcutaneous injection or anesthesia spray. Do not inject directly into the treatment site.



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