MyrliMax® and Low Back Pain: A Multicentric, Observational, Post-Marketing Surveillance Study in Indian Patients Suffering from Chronic Low Back Pain of Various Pain Intensity

Varun SUREJAa,*, Dharmeshkumar KHENIb, Divyanshu PRAJAPATIc, Mayank RAJAWATd, Ajit MAGARE, Asha KRISHNARAJe, Ashish SIRSIKARf, A ARUN PRASATHg, Amit MISHRAh, Anil Singh RAJPUTi, Balasubramanian VIJAYKRISHNANj, Chetan PURAMk, D MANOJ KUMARl, Diwakar AGARWALK, Girish SHIRAGAMBHAL, Jitendra PATILm, K RAVICHANDRANn, Kailash Nath JAINom, M THAYAGA RAUN, Rajesh ARORAp, S NAVAZISHQ, Sachin CHHABRAP, Lakshminarayan SHYAMR, Sudarshan ISs, Vinay AGGARWALT

aDepartment of Medical Affairs, Sundyota Numandis Group of Companies, Ahmedabad, India
bDepartment of Orthopedics, N.S.C.B Medical College, Jabalpur, India
cDepartment of Orthopedics, APJ Multi-Speciality Hospital, Walajabad, India
dDepartment of Orthopedics, Suchak Hospital, Mumbai, India
eDepartment of Orthopedics, Rajput Fracture, Joint & Trauma Clinic, Gwalior, India
fDepartment of Orthopedics, Lifespan Bone & Joint Clinic, Chennai, India
gDepartment of Orthopedics, Sancheti Institute for Orthopaedic & Rehabilitation, Pune, India
hDepartment of Orthopedics, Shri Kanaka Mahalaxmi Nursing Home, Vizag, India
iDepartment of Orthopedics, Diwakar Ortho & General Hospital, Jaipur, India
jDepartment of Orthopedics, Primus Hospital, Bengaluru, India
kDepartment of Orthopedics, Adarsh Nursing Home, Mumbai, India

Address for correspondence:
Varun SUREJA
Department of Medical Affairs, Sundyota Numandis Group of Companies,
7th Floor, 705-708 Tower A, Safal Pegasus, Pralad Nagar, Ahmedabad-380015, Gujarat, India
Mobile: +91 7878016065
Email: varun@sundyotanumandis.com

Article received on the 28th of December 2020 and accepted for publication on the 26th of February 2021
ABSTRACT

Background: Chronic low back pain (LBP) is the most common musculoskeletal condition affecting a person’s quality of life. Over the past decades, a lot of work was done in an attempt to reduce the negative impact of LBP, and help patients recover and maintain a better quality of life. Nevertheless, there is still a lot to be done to fully understand the problem of underlying chronic LBP and a wide gap that exist between basic science and applied rehabilitation research on LBP.

Objectives: This was an open label, multicentric, observational, post-marketing surveillance study in a real-world setup designed to evaluate the efficacy and safety of MyrliMax® capsules containing standardised Commiphora myrrha gum resin extract in Indian subjects with chronic LBP varying in intensity.

Material and methods: This study included 204 subjects diagnosed with chronic LBP at the outpatient department of 20 centres under the supervision of a medical doctor. All subjects took MyrliMax® capsules twice daily for 20 days. Visual Analogue Scale (VAS) pain score, rescue medicine requirement, therapy satisfaction scores and safety parameters were assessed as per the schedule.

Outcomes: Treatment with MyrliMax® capsules significantly (p<0.01) and progressively reduced the VAS score throughout treatment. A significant pain reduction was observed from the second visit. The mean VAS score was 6.58, 4.66, 2.99 and 1.88 on Day 0, Day 7, Day 14 and Day 20, respectively. A similar trend was also observed in subgroups based on gender and severity score. The need of rescue analgesics/NSAIDs was significantly reduced from the second week, indicating a potential of MyrliMax® capsules to increase the pain threshold. All physicians and patients were satisfied with the efficacy of MyrliMax® capsules assessed by physician’s satisfaction score and patient’s satisfaction score. There were no significant serious adverse events due to treatment during the study, which indicated that the treatment with MyrliMax® was well tolerated by subjects.

Conclusion: MyrliMax® capsule is a potentially effective and safe therapy for pain reduction in patients suffering from chronic LBP. MyrliMax® capsules can be used to reduce pain in NSAIDs intolerant subjects suffering from chronic LBP.

Keywords: MyrliMax®, Commiphora myrrha extract, chronic low back pain, furanodienes, analgesic.
INTRODUCTION

Chronic pain afflicts almost two billion people around the world (1). Low back pain (LBP) is defined as pain in the area of the posterior aspect of the body, from the lower margin of the 12th rib to the lower gluteal fold, that can relate to problems with the lumbar spine, discs between the vertebrae, ligaments around the spine and vertebral discs, spinal cord and nerves, muscles of the low back, internal organs of the pelvis and abdomen, or skin covering the lumbar area (2-4). Recurrent or chronic LBP (i.e., LBP persisting for 12 weeks or more) is a common problem, with an enormous individual, economic and societal burden (5, 6). Patients with LBP experience intense radiating leg pain that may be accompanied by neurological signs, associated with high healthcare costs, work absenteeism, and economic burden (7). Most of times, the optimal treatment is based on targeting the underlying mechanisms of pain and tailoring the management modality for each patient using a personalized approach (8); however, nonsteroidal anti-inflammatory drugs at the lowest effective dose with few recommendations on the use of combination drug therapy are also used (9).

However, long-term administration of non-steroidal anti-inflammatory drugs (NSAIDs) may lead to numerous complications, such as stomach ulcers, liver failure, and cardiovascular toxicity and many other adverse effects, including nausea, constipation, and the risk of dependency (10, 11).

The nutraceutical composition was provided as MyrliMax® capsules (Sundyota Numandis Pharmaceuticals Pvt. Ltd., Ahmedabad, India). Each delayed release gastro-protectant hydroxypropyl methylcellulose capsule contained 100 mg of C. myrrha powder extract (corresponding to at least 4 mg of bioactive furanodienes), along with other excipients, including microcrystalline cellulose, magnesium stearate, talc and silicone dioxide.

Identification of Commiphora myrrha extract furanodienes

One hundred milligrams of a C. myrrha powder extract were added in a glass tube with 5 mL of acetone:hexane in ratio of 1:1 (VWR International, Radnor, PA, USA) (extraction ratio 1:50 w/v) and 500 μg of internal standard (trans-nerolidol).
The samples were vigorously mixed by vortexing, and the powder was then extracted in an ultrasonic bath at 30°C for 30 min. At the end of the extraction, the samples were mixed by vortexing and centrifuged for 10 min at 5,000 g. The supernatant of the solvent was collected in a glass tube. Extraction was repeated twice, and the solvent aliquots were combined in the same glass tube, as previously described (14).

Prior to analysis, the extracts were loaded into Pasteur pipettes filled with MgSO4 (Fluka, USA) to filter the samples and remove any traces of water. The samples were then analyzed by gas chromatography (GC) coupled to mass spectrometry (MS) for qualitative analysis of the compounds and by GC coupled to a flame ionization detector (FID) for quantitative analysis. The GC-MS analyses were performed using an Agilent Technologies 6890N gas chromatograph coupled with an Agilent Technologies 5973A mass spectrometer using a Zebron ZB-5MS (Phenomenex, USA) capillary column (30 m length, 250 μm internal diameter, 0.25 μm film thickness). The injector temperature was set at 250°C, and a constant helium flow (1.0 mL min⁻¹) was used as the mobile phase. The following temperature program was used: initial temperature 50°C, followed by a linear thermal gradient of 3°C min⁻¹ up to 200°C and a second gradient of 10°C min⁻¹ up to 290°C. The final temperature was held for three minutes. The transfer line temperature to the MSD was 280°C, and the ionization energy (EI) was set at 70 eV with a full scan range of 50–300 m/z. The compounds were identified by comparing their mass spectra to the NIST 98 library using NIST mass spectral search software v2.0.

Quantitative analysis by GC-FID was performed using the same chromatographic parameters described above with the same type of column. The detector (FID) temperature was set at 280°C.

Study design
This was an open label, multicentric, single arm, observational, post-marketing surveillance study in a real-world setup.

Study duration and study centers
This study was conducted between the 1st of August 2019 and the 20th of December 2019 in discrete Indian centers.

Inclusion criteria
This study included both male and female subjects aged ≥18 years who were suffering from chronic low back pain varying in intensity.

Exclusion criteria
Subjects were excluded if they: 1) were suffering from unbearable acute pain; 2) were taking analgesic co-medication viz. antidepressants, hypnotics, muscle relaxants, anti-epileptics or corticosteroids; 3) had taken any long acting analgesics three weeks prior to enrolment; 4) had taken any short-acting analgesic viz. NSAIDs, peripheral analgesics, opioids, anaesthetics, or any other topical medication 24 hours prior to enrolment; 5) had any kidney or liver disorders; 6) had a history of epidural intervention exposure; 7) needed any other additional medication mentioned in the protocol; 8) had any hypersensitivity to the study drug; 9) were pregnant or lactating women; 10) were male and female subjects ≤18 years.

Methodology
Patients who attended the outpatient department of study centers and met the inclusion/exclusion criteria were considered to be eligible for the study. Demographic profile, medical assessments and evaluation parameters were recorded in a predesigned case record form (CRF) that was maintained for each subject. Eligible subjects were instructed by a medical practitioner to ingest MyrliMax® capsules as per the protocol. They were informed to take one capsule twice a day orally for 20 days and visit the study centre on days 0, 7, 14, and 20 in order to assess efficacy and tolerability parameters as per protocol. Efficacy evaluation was done by primary evaluation parameter, including measure of change in pain intensity assessed by VAS (numeric scale) on Day 0, Day 7, Day 14 and Day 20. The secondary parameter for efficacy assessment was the satisfactory score and requirement of rescue medicine. Safety and tolerability assessments were conducted by spontaneous reporting of directly observed adverse events after first dose until end treatment visit.

All subjects were advised to use NSAIDs/analgesics as a rescue medicine if required and they were asked to inform the study centre during their visit.
**Statistical analysis**

Data were expressed as mean±SD for pain scores as well as therapy satisfaction scores. Statistical analysis was performed using GraphPad Prism software version 8 (Graph Pad software, USA). The data of pain intensity in all subjects and subgroups were analysed using one-way ANOVA, followed by post-hoc analysis using Tukey’s multiple comparison test. A p-value <0.05 was considered statistically significant.

**OUTCOMES**

**Study material analytical results**

The bioactive components present in MyrliMax® capsules include curzerene, furanoeudesma-1,3-diene and lindestrene. These bioactive components are responsible for the analgesic action of the formulation. The identification and quantification as well as standardization of the bioactive furanodienes present in MyrliMax® capsules were performed using gas chromatography coupled to mass spectrometry (GC-MS) and gas chromatography coupled to a flame ionization detector (GC-FID), respectively, as per the procedure mentioned in the material and method section. These analytical results (Figure 1) have revealed that the total percentage of identified furanodienes was approximately 60% of the total volatile fraction, whereas the total furanodienes content was 40.89 gm per kg. These results are complying with the specification of active components given by the Biosfered S.r.l. (Turin, Italy).

**Clinical efficacy**

A total of 204 patients (117 women and 87 men) aged between 21 and 85 (female subjects: 21-85 years; male subjects: 22-81 years), with a mean age of 49.69±13.73 years (female subjects: 50.59 ±13.13 years; male subjects: 48.51±14.49 years) were included in the study as per the inclusion and exclusion criteria. Table 1 lists the centers participating to the study and the number of enrolled female and male volunteers, and dropouts. Subjects’ pain intensity was evaluated using VAS pain score 0-10. Subgroup analysis was conducted based on gender as well as severity score at the time of inclusion (i.e., severe pain with a VAS score 7-10; moderate pain with a VAS score 4-6; and mild pain with a VAS score 1-3). Table 2 summarizes the pain score subdivision according to pain severity.

The results of our multicenter pilot study are represented in Figure 2, where data are depicted by considering both total sample data and subgroup data based on gender and pain severity. In

**FIGURE 1.** Analytical results confirming the presence of bioactive components in MyrliMax® capsules
particular, there was a significant (p < 0.01) decrease in pain score values for the entire population (N=204), with a progressive reduction in pain when MyrliMax® was administered. The general data for “male” and “female” subgroups showed the same decreasing trend in pain score, with no significant differences between male and female populations. With regard to pain severity, all subjects experienced a reduction in pain; thus, at the end of the administration period (day 20) there was a 73% reduction in the subgroup with initial “severe” pain, a 69% reduction in the subgroup with initial “moderate” pain, and a 90% reduction in the subgroup with initial “mild” pain. When considered separately, female subjects with initial “severe”, “moderate” and “mild” score showed pain reduction by 71%, 67% and 89%, respectively, whereas male subjects with initial “severe”, “moderate” and “mild” score showed pain reduction by 75%, 72% and 90%, respectively. Overall, both general and subgroup data showed similar trends in pain reduction.

We then assessed the level of therapy satisfaction in both enrolled subjects and curing physicians by setting a scale on which 0 meant lack of satisfaction, 1=poor satisfaction, 2=satisfaction and 3=high satisfaction. Figure 3 shows the result of this investigation, with a total value of almost 2.5 for the enrolled subjects and no significant differences (p> 0.10) in the responses of male and female subjects. Interestingly, the same value was recorded for physicians, with no statistical differences (p > 0.3) between physicians and subject responses.

Additionally, we evaluated each subject’s opinion on MyrliMax® with respect to product ef-
MyrliMax® - a Natural Analgesic for Chronic Low Back Pain

FIGURE 2. VAS pain scores (mean±SD) for female, male and female + male subjects during the 20 days of MyrliMax® administration; *significant (p <0.01) differences with respect to day 0

A minority of the general population (5%) was poorly satisfied, whereas only one subject was not satisfied. The separation of population data based on gender showed a higher satisfaction for males (62%) when compared to females (49%); the latter also showed a lower percentage of subjects...
MyrliMax® - a Natural Analgesic for Chronic Low Back Pain

Finally, the average number of rescue medicine units consumed per subject during particular periods of study (first week, second week and third week) were also evaluated. The findings were summarized in Table 3, where subjects required rescue medicine support during the first week of therapy, and this requirement gradually reduced during the following weeks. Male subjects needed less rescue medicines during second week compared to female subjects. This observation is in line with the general assumption about sensitivity of women towards pain. Results also highlight a potential requirement for rescue medicines during early 2-4 days while on MyrliMax® capsule therapy. Reduction in rescue medicine requirement during weeks 2 and 3 of MyrliMax® capsule therapy may point to a reduced need or dependency on synthetic pharmaceutical dosages. In most cases, the rescue medicines included Paracetamol, NSAIDs (Ibuprofen/Diclofenac/Aceclofenac) or Tramadol.

Tolerability

There were no reports of significant serious adverse events due to study treatment, which indicated that the treatment with MyrliMax® was well-tolerated by participants. Few mild side effects were observed in eight patients, including mild nausea (n=4), vomiting (n=2), and loose motion (n=1). Also, one patient showed symptoms of vertigo. However, these side effects occurred during the early course of therapy in most cases, and none of the observed side effects disrupted treatment. Seven dropouts occurred during the study, which were not correlated to treatment induced side effects or tolerability issues.

DISCUSSION

Evidence on efficacy of C. myrrha (Myrrha, Syn. C. molmol) gum resin extract in treatment of discrete pain types have been scrutinized in several clinical studies. C. myrrha contains a bioactive component, furanodienes, which shows analgesic and anti-inflammatory actions. The furanodienes component (curzerene and furanoede-sma-1, 3-diene) of C. myrrha was reported to exert an analgesic activity by interacting with opioid receptor, which was confirmed by reversal of this action by naloxone (13). Myrrh had been also reported to have a potential role on inflammatory targets such as COX, NO formation, ROS, TNF-α, PGE-2, NF-κB, MAPK, and it was showed to have an anti-inflammatory action (15). A prospective open label study for prophylaxis of migraine reported the effectiveness of C. myrrha treatment because of its analgesic and anti-inflammatory activities (16). A long-term pilot study with a duration of six months was conducted in patients suffering from migraine without aura or tension type headache. In this study, patients received a nutraceutical-based combination containing MyrLiq®, a highly standardized gum resin extract of C. myrrha, which was found to lead to an improvement in pain and a significant reduction in the levels of several cytokines.

![FIGURE 3. Therapy satisfaction scores (mean±SD) of MyrliMax® capsule administration in subjects and physicians expressed as 0=not at all satisfied; 1=poorly satisfied; 2=satisfied; 3=highly satisfied. Metric bars represent standard deviation (SD).](image)

![FIGURE 4. Subjects' opinion – total and gender-based satisfaction of MyrliMax® capsule efficacy expressed as percentage values declaring a poor satisfaction and no satisfaction (six and two subjects, respectively).](image)

![TABLE 3. Average number of rescue medicine units consumed per subject during the study](table)
MyrliMax® - a Natural Analgesic for Chronic Low Back Pain

(IL-6, IL-8 and TNF-α). This study also reported the safety of C. myrrha extract for a longer period of time (17). Nutraceutical supplement containing C. myrrha was reported to improve various types of tendinopathies when administered along with extracorporeal shock wave therapy (ESWT). The results of this study showed the effectiveness of supplement containing myrrh in faster pain relief, which was evaluated by VAS score. Also, no side effects were observed with the administration of nutraceutical supplement (18). A pilot study on the analgesic effects of highly standardized gum resin extract of C. myrrha with a high furanodienes content reported pain alleviation at 400 mg and 200 mg in various etiologies of pain. In this study, a dose of 400 mg per day was effective in all kinds of pain, whereas 200 mg per day alleviated only low back pain in male subjects and fever dependent pain in all patient, showing its significant analgesic properties (14). Also, C. myrrha extract showed efficacy in reducing the number of days with headache, average pain intensity and analgesic consumption when combined with Ginkgo biloba, CoQ10 and riboflavin in women suffering from menstrual migraine (19). In women suffering from endometriosis, C. myrrha extract in combination with alpha-lipoic acid and palmitoylethanolamide led to a significant reduction in pain symptoms including dyspareunia, dysmenorrhoea and chronic pelvic pain (20). In patients suffering from chronic pain affecting muscles, joints or the back due to sports trauma or advanced age, C. myrrha extract was found to determine a significant reduction in pain perception (just within three days) as well as loss of functions, with good tolerability profile (21). In patients with mild osteoarthritis, C. myrrha extract in combination with chondroprotective agents such as glucosamine, chondroitin, curcuma and bromelain led to a significant reduction in joint pain and stiffness. In this study, the intervention period of six months indicates the safety of oral C. myrrha gum resin extract for long-term use (22). In patients with recurrent uncomplicated urinary tract infections, C. myrrha extract is useful in preventing symptomatic urinary tract infection episodes and improves quality of life (23). In patients with symptoms of acute diarrhoea, C. myrrha extract in combination with coffee charcoal and chamomile flower extract showed its efficacy and safety (24). C. myrrha extract was found to be effective in reducing mild to moderate chronic pain in elderly population when combined with Piper nigrum and Rosmarinus officinalis (25). The fact that C. myrrha extract did not cause any significant side effects even at a higher dose of 11.5 mg/kg body weight per day on liver and kidney function test indicates its safety even at a higher dose (26).

Although many trials confirmed the efficacy of C. myrrha extract, there were no clinical studies in Indian population. Our study was an open label pilot study that demonstrated the efficacy of MyrliMax® capsules containing a highly standardized extract of C. myrrha in gastro protectant delayed release capsule in Indian patients suffering from chronic low back pain. In this study, quantitative and qualitative standardization of the extract for bioactive furanodienes was done using GC-MS and GC-FID. Our findings were consistent with those provided by previous studies and confirmed the effectiveness of C. myrrha extract as an analgesic agent. The results of the present study reported a significant reduction in pain scores at every treatment interval in both overall population and subgroups (based on “severity” and “gender”). Therapy satisfaction was assessed for both patients and physicians and showed a high level of satisfaction, with no significant differences between patient and physician scores, as highlighted in Figure 2. This study also showed that the administration of MyrliMax® capsule could reduce concomitant use and need of other rescue medication required for pain. Safety assessment showed the better tolerability of the MyrliMax® capsule. Collectively, the results of present study highlight the effectiveness and safety of MyrliMax® capsule in alleviating LBP of different intensity. We believe that the significant efficacy of MyrliMax® capsules observed in this study at lower dose is due to the usage of gastro-protectant delayed release capsule dosage form that prevents gastric interaction of bioactive furanodienes and allows its release in intestinal fluid for further absorption and biological actions.

CONCLUSION

MyrliMax® capsule is a potentially effective and safe therapy for pain reduction in patients suffering from chronic low back pain. Since an open label, non-randomized, non-controlled design may be a major limitation of this trial, ran-
domised trials with controlled designs are needed to further explore the wider role of C. myrrha extract based formulations in the management of chronic painful inflammatory conditions.

Conflicts of interest: Varun SUREJA, Dharmeshkumar KHENJ, Mayank RAJAWAT and Ajit MAGAR are employees of Sundyota Numandis Group of Companies. Divyanshu PRAJAPATI and Asha KRISHNARAJ were employees of Sundyota Numandis Group of Companies during the course of this study.

Financial support: none declared.

Acknowledgements: We acknowledge the support of Professor Massimo Maffei, University of Turin, Italy, for his advice in preparing the manuscript. We are grateful to late Dr. Virat Chavan-Parvatibai Chavan Charitable Trust, Mumbai, for his contribution to conducting this study.

References


