AXSAIN CREAM 0.075%

CLINICAL EXPERT REPORT

PERIPHERAL DIABETIC NEUROPATHY

10670/0010

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PRODUCT PROFILE - AXSAIN CREAM 0.075%

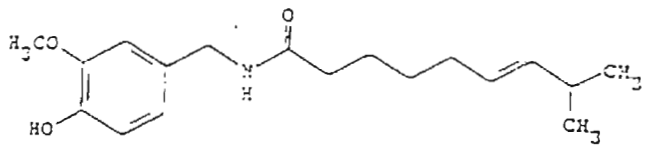
A. TYPE OF APPLICATION

This is a medically targeted, abridged product licence application for marketing authorisation in the United Kingdom for Axsain Cream 0.075% under PL 10670/10. This application cross-refers to an existing product licence held by Euroderma Ltd for Axsain Cream 0.075% PL10670/0003, which is indicated in the management of post-herpetic neuralgia and was approved on 20/8/1992.

Axsain Cream contains 0.075% capsaicin, a naturally occurring substance found in capsicum fruit.

B. CHEMICAL AND PHARMACOKINETIC PROPERTIES

Capsaicin, chemical name trans-8-methyl-N-vanillyl-6-nonenamide, is an alkaloid with the following structure:



Capsaicin has a molecular weight of 305.40 and forms white translucent crystals which melt at 64.5°C.

Absorption after topical application is unknown. Average consumption of dietary spice from capsicum fruit has been estimated as 2.5g/person/day in India and 5.0g/person/day in Thailand. Capsaicin content in capsicum fruit is approximately 1%, therefore daily dietary intake of capsaicin may range from 0.5-1mg/kg/day for a 50kg person. Application of two tubes of Axsain cream 0.075% (90g) each week results in a 9.6mg/day topical exposure. Assuming 100% absorption in a 50kg person, daily exposure would be 0.192mg/kg, which is approximately one-third to one-quarter of the above-mentioned dietary intake.

C. INDICATIONS

Axsain Cream 0.075% is indicated for the symptomatic management of painful diabetic peripheral polyneuropathy.

Although the precise mechanism of action of capsaicin is not fully understood, evidence suggests that capsaicin renders skin insensitive to pain by depleting and preventing subsequent reaccumulation of Substance P in peripheral sensory neurons. Substance P is one of the principal chemomediators of pain impulses from the periphery to the central nervous system and also plays a role in inducing inflammatory response.

Adults and elderly should apply Axsain Cream 0.075% to the affected area not more than 3 to 4 times daily. Axsain is not suitable for use in children.

D. PRECAUTIONS

Axsain Cream 0.075% is contra-indicated on broken skin or irritated skin. It should be kept away from the eyes. After applying Axsain cream with the fingers, hands should be washed immediately.

Axsain may cause transient burning on application. This burning is observed more frequently when application schedules of less than 3 to 4 times daily are utilised.

E. MARKETING/POST-MARKETING

Axsain Cream 0.075% is licensed for the symptomatic relief of pain associated with post-herpetic neuralgia in the UK, and is approved for symptomatic management of painful diabetic peripheral polyneuropathy in the US, Canada, Australia and Eire.

1. PROBLEM STATEMENT

In patients who fulfil the accepted criteria for the diagnosis of diabetes mellitus, clinical diabetic neuropathy is defined as symptoms of peripheral nerve damage and dysfunction associated with abnormal signs and symptoms and/or abnormal objective measurements with no evidence of other hereditary or acquired causes of neuropathy. Peripheral neuropathy is one of the most common and debilitating complications of diabetes mellitus. The prevalence of peripheral diabetic neuropathy is not well established, but may be as high as 80% when subclinical cases are included (1,2). In a 25-year prospective study of 4400 patients, 12% had clinical neuropathy at the time diabetes was diagnosed which increased to 50% after 25 years of diabetes (3). In the 1989 U.S. National Health Interview Survey (NHIS), 2405 diabetic subjects were questioned on whether they had experienced symptoms of sensory neuropathy in the previous three months (4). Among these individuals, 28.2% reported numbness, 26.8% reported pain or tingling, and 9.8% reported decreased ability to feel hot or cold.

Peripheral diabetic neuropathy consists of a variety of specific syndromes with different clinical courses and most likely different pathogenic mechanisms. Classification of diabetic neuropathy is largely a function of which neuronal populations are involved; e.g., autonomic or somatic neurons, motor or sensory neurons, and according to the neuroanatomical site of the lesion; either diffuse or isolated (See Table 1).

Table 1: Classification of diabetic neuropathy

Polyneuropathy
- distal symmetrical polyneuropathy - autonomic neuropathy
Isolated (focal and multifocal) Neuropathies
- Mononeuropathy - Mononeuropathy multiplex - Radiculopathy - Entrapment neuropathy - Cranial neuropathy - Proximal amyotrophic neuropathy

The most widely recognized and probably the most common form of diabetic peripheral neuropathy is distal symmetrical polyneuropathy. This disorder entails a heterogenous range of clinical features such as dysesthesias, paresthesias (tingling, numbness, and burning pain), and pruritus with altered vibration, temperature, position and touch perception. The onset of distal symmetrical polyneuropathy is usually insidious occurring in a "stocking-and-glove" distribution with the feet being primarily affected. The primary complaint is pain. Contact discomfort (allodynia) is also characteristic, such that patients cannot bear the soreness caused by shoes and socks and bed covers. Symptoms tend to be worse at night and can lead to insomnia and depression.

Contemporary therapeutic or preventative approaches to diabetic neuropathy fall into three general categories: [1] improved metabolic control, [2] drug therapy to prevent or reverse the condition and, [3] alleviation of distressing symptoms such as pain (1,2). While the specific causes of diabetic neuropathy are not fully understood, there is general agreement that the most effective method to prevent or halt the progression of neuropathy is to reduce and stabilize blood glucose levels as close as possible to normal physiological levels. This concept is strongly supported by the recent Diabetes Control and Complications Trial (DCCT) completed in 1993. In the DCCT study, there was a 60% reduction in the risk of development and progression of neuropathy with "tightly" controlled blood glucose levels when compared to what had historically been normal, but less rigorous, control of hyperglycaemia in diabetic individuals (5). The degree to which tight blood glucose control can reverse neuropathic damage remains to be proven. In patients whose diabetes has been poorly controlled, better control of blood glucose levels may cause relief of neuropathic symptoms including pain. Unfortunately, this is not true for all cases. While tight diabetic control can prevent the neuropathy from worsening, it does not consistently relieve existing pain. Insulin, when given as a continuous intravenous infusion over a period of one to two days, may break the cycle of pain in some patients through an unknown mechanism, but apparently unrelated to the control of blood glucose concentrations (1,2).

Although extensive research efforts have been focused on the development of pharmacological agents that interfere with the pathological processes that cause diabetic neuropathy, no therapeutic modalities are currently available. A partial list of drugs in development include; aldose reductase inhibitors, nerve growth factors, insulin-like growth factors, and gangliosides (2).

Drug therapy for pain associated with diabetic neuropathy has come to rely on tricyclic antidepressant and anticonvulsant medications. Most of the evidence accumulated to date indicates that tricyclic antidepressants exert a direct analgesic effect, independent of antidepressant activity, in a number of chronic pain states. Nearly fifty well-controlled clinical studies have been conducted on the effects of tricyclic antidepressants for the treatment of chronic pain conditions, including five trials in painful diabetic neuropathy (6). In general, fifty percent or more of the patients suffering from neuropathic pain obtained at least some pain relief. These agents appear to be most effective in patients with dysesthetic pain. The choice of one particular tricyclic antidepressant over another is largely an empirical decision. Amitriptyline is currently the most studied and widely used of the antidepressants for the treatment of neuropathic pain. Anticholinergic effects, postural hypotension and CNS adverse effects can limit the usefulness of these drugs in diabetic patients (1,2,6-8).

Controlled clinical studies indicate that the anticonvulsants, carbamazepine and phenytoin, act to provide relief of pain associated with diabetic neuropathy. However, adverse effects also limit the therapeutic usefulness of both agents and their use is controversial among pain management experts (1,2,7,8). When tricyclic antidepressants or anticonvulsants alone fail to provide adequate pain relief, combination therapy and other therapeutic options are considered (6-8). These include neuroleptics, Type IB antiarrhythmics (mexiletine, tocainide, and lidocaine), clonidine, and nonarcotic or opioid analgesics. The management of neuropathic pain with opioid analgesics has been approached cautiously due to concerns about the development of tolerance, potential adverse effects, serious toxicity, habituation, as well as questions

concerning efficacy. Non-narcotic analgesics such as acetaminophen, or various nonsteroidal anti-inflammatory drugs are generally ineffective for the relief of pain associated with diabetic neuropathy (1,2,6-8).

Axsain cream containing 0.075% capsaicin has been shown to be useful in the symptomatic relief of pain associated with diabetic neuropathy and will be a valuable addition to the physician's armamentarium for the treatment of this condition. Axsain is a safe and effective topical analgesic therapy for patients requiring relief from painful diabetic neuropathy as demonstrated in well controlled clinical trials. Axsain has also been shown to enhance a patients' quality of life by reducing pain and improving their ability to carry out their routine daily tasks. Capsaicin, the active ingredient in Axsain produces an analgesic effect by interfering with the synthesis, storage, transport and release of Substance P from nociceptive C-fibre neurons. Axsain selectively relieves neuropathic pain without interfering with normal CNS functions. Furthermore, Axsain does not interfere with sensory perception from the treated area, which may already be impaired in the patient with diabetic neuropathy. Axsain poses minimal risk to the patient with painful diabetic neuropathy. Axsain is a topical medication with low systemic absorption, there are no known systemic adverse reactions or drug interactions. The apparent lack of systemic activity takes on an added measure of importance in the diabetic patient, whose health and general well-being may already be compromised by diabetes and/or any one of many long term complications associated with the disease. When necessary, other medications used to manage the pain of diabetic neuropathy or associated conditions such as depression, or drug therapy for completely unrelated conditions, can be administered concurrently with Axsain without concern for drug interactions.

Topical capsaicin has been shown to be safe and effective analgesic therapy and has gained wide spread use in the U.S. and Canada as pain management therapy for the treatment of arthritis, painful diabetic neuropathy, and postherpetic neuralgia. Axsain cream (PL 10670/0003) was licensed in the UK in 1992 for the symptomatic relief of neuralgia associated with and following herpes zoster infections (post-herpetic neuralgia), after open lesions have healed. Clinical data are presented in this application supporting the safety and effectiveness of Axsain for the symptomatic relief of the pain associated with diabetic neuropathy.

2. CLINICAL PHARMACOLOGY

2.1. Neuropharmacology

Comprehensive reviews on the neuropharmacology of capsaicin principally from *in vitro* assessment and animal experimentation can be found in the medical literature. Full copies of two reviews (9,10) are included in Appendix 5 of this report.

Pain is mediated by nociceptors. Morphologically, nociceptors are free nerve endings of primary afferent neurons which are activated by various forms of injury such as strong mechanical stimulation, heat or certain chemicals. Nociceptors generate an impulse when the threshold for a particular stimulus has been reached. Nerve fibres convey the information of an injury not only as a quantified signal, but also differentiated according to the type of injury. Abrupt and sharp injury to the skin, muscle, or articular tissue is transmitted by myelinated A-delta nerve fibres. The other type of pain, often characterized as a burning sensation resulting from prolonged tissue

damage, is mediated by unmyelinated nociceptive C-fibres which are polymodal in the sense that they respond to chemical, thermal and mechanical injury.

The undecapeptide Substance P is believed to be a principal neurotransmitter involved in the transmission of noxious stimuli and is found predominately in nociceptive C-fibres and to a lesser extent, A-delta fibres (11). It is thought that Substance P is an excitatory neurotransmitter at central terminals of primary afferent neurons located in the dorsal horn of the spinal cord. Intraspinal injections of small doses of Substance P cause a pain reaction in mice and microinjections of Substance P in the dorsal horn cause an increase in activity of spinal cord projection neurons (12,13). Primary afferent C-fibres are also capable of releasing Substance P at their peripheral nerve terminals. Once released, Substance P causes vasodilatation, plasma extravasation, and release of histamine from mast cells (14). In animal preparations, locally applied capsaicin appears to preferentially affect nociceptive C-fibres and to a lesser extent A-delta fibres (9,15).

Capsaicin has an immediate excitatory effect on afferent neurons and has been shown to produce a depolarization of nociceptive C-fibres when studied using cultured neuronal preparations (16,17). In man, this activity is exemplified by observations that local applications of capsaicin produce an immediate effect of burning pain and/or marked hyperalgesia presumably by activation of primary afferent C-fibres and perhaps A-delta fibres and release of Substance P (18).

Accompanying capsaicin-induced depolarization is an increase in the neuronal membrane permeability to cations particularly calcium and sodium ions as evidenced by voltage-clamp and patch-clamp methodology (19). The degree of excitability and sensitivity of sensory neurons to capsaicin is regulated by nerve growth factors (20). The membrane ion channel activated by capsaicin is unique and is insensitive to conventional calcium and sodium ion channel blockers such as the dihydropyridines (16). Capsaicin-induced depolarization of nociceptive neurons is likely to be the result of an interaction with a specific membrane receptor. Recent evidence confirming the existence of a capsaicin receptor, localized to mammalian sensory neurons, has been obtained using a novel capsaicin competitive antagonist, capsazepine (21).

An important aspect of capsaicin-induced depolarization of nociceptive sensory neurons is the release of Substance P and other neuropeptides from peripheral and central nerve terminals (22). It is likely that capsaicin-evoked Substance P release is due entirely to calcium entry via receptor activated calcium channels (17). This mechanism may contribute to the antinociceptive or analgesic effect of capsaicin.

With repeated exposure to capsaicin, there is desensitization of both the nociceptive C-fibre activation and the peripheral analgesic effect. The extent of desensitization depends on the concentration of capsaicin and time of exposure. Low concentrations of capsaicin induce a loss of sensitivity to further capsaicin administration without impairing responses to other noxious stimuli (17). Conceivably, this desensitization process may involve affinity changes in the capsaicin receptor or uncoupling of the receptor-ion channel complex.

Exposure of peripheral nerves to capsaicin produces a prolonged block of conduction in nociceptive neurons and a loss of chemical sensitivity due to impairment of signal transduction at the nerve terminal (18). This nonspecific desensitization is exemplified

by a loss of sensitivity to capsaicin and attenuated responses to other chemical and physical noxious stimuli. For example, a 33 mM concentration of capsaicin applied five to ten times over the course of a few hours to the eye of the rat and guinea-pig (23,24), to the human tongue (25), and to intact skin (26,27) elicited a selective, reversible loss of sensation. Pain induced by noxious heating or provoked by chemical agents as well as itch and warmth sensations were impaired. In contrast, tactile sensations, pricking pain, and cold sensations were unchanged. In human skin, axon reflex flare elicited by cutaneous electrical stimulation (28) or a chemical agent (29) was abolished by topical capsaicin, the later at concentrations of 3.3 mM. The selective sensory loss and inhibition of cutaneous sensory flare were fully reversible. Finally, desensitization may be the result of selective sensory neurotoxicity brought about by toxic concentrations of capsaicin (10). Histopathologically, osmotic changes and axonal swelling are evident along with swelling and disruption of mitochondria and other intracellular organelles (9,15). These neurotoxic actions appear to be unrelated to the antinociceptive action of capsaicin since this latter effect is readily reversible and occurs without evidence of neurodegeneration.

In rats, systemically administered capsaicin at high doses caused a gradual depletion in the Substance P content of nociceptive neurons. Substance P in dorsal roots, nerve, and skin began to fall five hours after a 50 mg/kg subcutaneous dose and fell to a level of 60-70% of control at day 4 (30). After a 125 mg/kg subcutaneous dose, the recovery of Substance P levels was regional. The saphenous and other nerve levels were normal after 1 month, but the dorsal root ganglion and dorsal root levels did not return to normal for 4 months and the spinal cord levels still had not reached pretreatment levels after 9 months (23). One possible mechanism whereby capsaicin may reduce neuronal concentrations of Substance P relates to the action of capsaicin as a blocker of axonal transport of peptides in C-fibres (31). Substance P is depleted only in primary afferent sensory neurons, not in Substance P-containing neurons of the gut or central nervous system. However, capsaicin is not selective for Substance P depletion and produces marked reductions in a number of other neuropeptides, including somatostatin, calcitonin gene-related peptide, and vasoactive intestinal polypeptide (18).

The depletion of Substance P in primary nociceptive neurons has been shown to have functional consequences. The sensitivity to pain stimuli is reduced in various animal preparations. Additionally, after capsaicin treatment, antidromic vasodilatation, reactive cutaneous hyperemia, and flare due to axon reflex are abolished, suggesting that substance P-depleted neurons have reduced neurotransmitter release not only from central, but also from peripheral nerve terminals (14).

The antinociceptive effects of long-term topical application of capsaicin have been evaluated in animal models and normal human subjects. The functional status of afferent C-fibres was markedly reduced following topical application for 10 consecutive weeks of two capsaicin dosages (0.075% and 0.75%) twice daily to the hind paws of rats (32). The impairment of neurogenic extravasation by the two doses was not significantly different. Complete recovery was noted at four weeks post-application in the lower dose group whereas only partial recovery was evident at 12 weeks post-application in the high dose group. There were no significant changes in the neuropeptide levels and the dorsal root ganglion cell counts did not reveal a significant degree of neurotoxicity with either dose.

In a double-blind clinical investigation, ten normal human volunteers applied 0.025% capsain to one arm and a control emollient on the contralateral arm four times daily for a period of two weeks (33). Skin temperature; skin temperature change and flare generated by histamine and allyl isothiocyanate; tactile threshold; sensitivity to heat, cold, and pinprick intensity; galvanic skin potential amplitudes (GSP); electrical stimulation perception thresholds (ESP); and antidromically-evoked sensory nerve action potentials (SNAPs) were determined at baseline, and at three hours, three days, and 14 days of application. There were no significant changes in GSP, skin temperatures or to tactile thresholds, ESP or SNAPs. Perceived intensity of grouped hot, cold, and pinprick stimuli was significantly diminished by the repeated application of capsaicin. After 14 days of application, heat sensation was preferentially affected, with only borderline effects on pinprick and cold sensation. Flare responses were not diminished in this study even after repeated applications and despite a small sensory loss.

In another double-blind study conducted with ten normal human subjects, Axsain was compared to vehicle cream when applied to the forearm four times daily for a period of six weeks (34). Psychophysical measurements of detection thresholds and suprathreshold magnitude for several cutaneous sensory modalities were made within each treatment area at baseline and one, three, and seven days after the first application and once per week thereafter. During the first two to five weeks, Axsain evoked mild burning pain, but no visible flare, with each application. No adverse sensations were reported with the vehicle cream. Neither tactile detection thresholds nor pain sensation induced by pricking or pinching were altered by Axsain or vehicle. Warmth sensation thresholds increased significantly during the later stages of the study. A return to baseline was noted within two weeks post-application. Heat pain threshold increased after two weeks of application and remained elevated. A maximum increase of 22.8% (vs. 3.5% for vehicle alone) occurred at the end of the study. Within two weeks of post-application, the mean pain threshold began to return to baseline. The sensation of itch produced by histamine was not affected by Axsain treatment. These results demonstrate that prolonged application of capsaicin diminishes selectively sensations of heat pain. This effect is temporary, but is maintained with repeated Axsain application.

The effect of Axsain (0.075%) on the thermal and vibration thresholds was examined in 22 subjects with diabetes mellitus and painful diabetic neuropathy participating in an eight-week, double-blind, vehicle-controlled trial with a follow-up 48-week open-label treatment period (35). All subjects underwent quantitative sensory testing for determination of cold, warm, and vibration thresholds at baseline and after eight weeks of treatment. Patients who continued to participate in the open-label portion of the study were also evaluated after 24 and 32 weeks of treatment. Sensory thresholds were determined in all subjects at the site of Axsain or vehicle application.

Baseline sensory thresholds for warm, cold, and vibration sensations were significantly reduced in both groups when compared to values typically exhibited by normal nondiabetic control subjects. There was no significant change in the mean warm, cold, or vibration threshold between baseline and the eight-week visit in either group. When the mean change in cold threshold was examined for the two groups jointly, a significant reduction ($p=0.04$) was detected after eight weeks when compared to baseline, implying an increased sensitivity to cold. This observation may be due to increased sensitivity of cold receptors associated with vasodilation and warming of the

skin produced by application and rubbing of the creams. In the subjects participating in the open-label phase of the study (n=170), no effects on warm, cold, or vibration thresholds were detected with up to 32 weeks of capsaicin treatment. The results obtained with capsaicin (0.075%) in diabetic subjects agree with those in normal nondiabetic subjects and suggest that there is minimal adverse action of topical capsaicin (0.075%) on the function of unmyelinated Type-C fibres subserving warm sensation, A-delta fibres conveying cold, and large myelinated A-fibres transmitting vibration and other sensory modalities.

2.2. Pharmacokinetics

Systemic absorption following the topical application of 0.075% capsaicin as Axsain has not been studied. However, systemic and distant somatosensory activity has not been observed after local applications implying that systemic absorption from cutaneous vascular beds is low. Moreover, daily exposure from topical therapy is considered to be much less than the amount ingested based on the average consumption of dietary spice from capsaicin fruit. For example in some parts of Asia it is estimated that a highly spiced diet could contain 0.5-1.0 mg capsaicin per kilogram body weight per day (36).

No information is available concerning absorption, distribution, metabolism, or elimination following either oral or systemic administration in man. After intravenous administration to rats, capsaicin is concentrated mainly within the spinal cord and the brain, and to a much lesser extent in the liver and blood. At an intravenous dose of 1 mg/kg, the half-life of capsaicin in rats was 7.1±3.2 min (mean±SD, n=4) (37). When capsaicin was administered orally to rats, about 85% of the dose was absorbed over the course of three hours and was largely converted to dihydrocapsaicin by first pass metabolism (38). Both capsaicin and the metabolites of capsaicin bind to serum albumin and both are metabolized in the liver by the mixed function oxidase system. Dihydrocapsaicin and capsaicin are believed to be excreted in the urine (38,39). The significance of these findings to absorption, metabolism, distribution, and elimination of capsaicin in man is unknown.

Capsaicin has no known drug interactions and seemingly low systemic levels following topical application further minimizes this potential.

3. CLINICAL TRIALS

Four clinical trials are reported, three of which were double-blind and the fourth was open label investigation. Brief details are given in Table 2 overleaf. A comprehensive tabulated description of these studies is provided in Appendix 3 and a tabulated summary of each study is provided in Appendix 4.

Table 2: Summary of clinical trials

Study No. and/or publication	N	Study Description	Objectives
#87-01 (40) Chad *et al* (43)	58	Comparison of capsaicin (0.075%) to vehicle	Safety and efficacy
#88-17 (41) Donofrio *et al* (44) & Dailey *et al* (45)	277	Comparison of capsaicin (0.075%) to vehicle	Safety, efficacy, quality of life, long-term effects (subset analysis), sensory effects (subset analysis)
#89-02 (42) (unpublished)	235	Comparison of capsaicin (0.075%) to amitriptyline (25-125 mg); followed by combination therapy	Safety, efficacy, quality of life
Pfeifer *et al* (46)	75	Evaluation of capsaicin (0.075%), stretching alone or with metaxalone ± piroxicam; or imipramine ± mexiletine;	Efficacy of treatment regimen based on type of pain experienced

3.1. Assessment of Individual Studies

Study #87-01: This multicentre study was carried out in 58 patients with painful distal symmetrical polyneuropathy. All patients had stable and well-controlled diabetes with daily, moderate to severe pain assessed by standard scales for pain severity; 54 patients reported tingling paresthesia and 44 patients noted nocturnal exacerbation of pain. By neurological examination, all patients had evidence of distal symmetrical polyneuropathy with sensory loss, and eight patients had mild to moderate distal leg muscle weakness. Standardized nerve conduction testing with measurement of surface temperature was performed in 51 patients. Median nerve measurements included distal motor latency and motor conduction velocity, F-wave latency, and orthodromic sensory conduction velocity. Peroneal nerve studies included the distal motor latency, motor conduction velocity and F-wave latency. Measurement of sural nerve antidromic conduction velocity was also made. Forty-three out of fifty-one patients had abnormalities on nerve conduction tests, confirming the presence of a

polyneuropathy by that measurement. In eight patients, nerve conduction studies were normal. The study was conducted in accordance with good clinical practice.

Patients were randomized to receive either Axsain (0.075% capsaicin) or vehicle cream for four weeks. Of the forty-six patients who completed the study, twenty-four received capsaicin and twenty-two received vehicle. Study medication was applied to painful areas four times a day for the duration of the study.

Due to violations of study protocol, twelve patients (five from the capsaicin group and seven from the vehicle group) were excluded from data analysis.

Pain severity and pain relief were measured after two and four weeks of treatment using both categorical and visual analogue scales (VAS). The results obtained with each pain scale, expressed as a percent improvement from baseline after four weeks of therapy are shown in Table 3.

Table 3: Results of study 87-01

Pain Scale	Mean Percentage Improvement	
	Capsaicin (n=24)	Vehicle (n=22)
Physician's Global Evaluation	66 (2 weeks) 71 (4 weeks)	45 (2 weeks) 50 (4 weeks)
Pain Severity Scale	49 (2 weeks) 67 (4 weeks)	40 (2 weeks) 46 (4 weeks)
VAS-Pain Severity	50 (2 weeks) 71 (4 weeks)	38 (2 weeks) 45 (4 weeks)
VAS-Pain Relief	63 (2 weeks) 71* (4 weeks)	33 (2 weeks) 41 (4 weeks)

* $p<0.05$, logistic regression analysis

Despite a relatively small number of subjects, the results strongly imply a beneficial effect of Axsain in the relief of painful diabetic neuropathy. There was a consistent improvement in all scales from Week 2 to Week 4 in the Axsain-treated group while the vehicle group remained essentially unchanged. The percentage of patients showing improvement after 4 weeks of treatment tended to be greater for Axsain cream on all 4 pain scales with a statistically significant change occurring in the VAS-Pain Relief analysis (71% reduction vs 41%, $p<0.05$).

Study #88-17: This large multicentre trial was conducted in 277 patients with painful symmetrical polyneuropathy (247 patients), radiculopathy (20 patients), or both distal symmetrical polyneuropathy and radiculopathy (10 patients). Patients applied Axsain cream or vehicle four times daily for a period of eight weeks. Two hundred nineteen patients completed the study. After the double-blind period, a subset of 18 patients were placed on Axsain cream in an open-label fashion for an additional follow-up period ranging from two to 48 weeks (mean, 22 weeks).

The diagnosis of distal symmetrical polyneuropathy or radiculopathy was established based on a history consistent with neuropathic pain, results of neurological examination, and an abnormality in at least one nerve during nerve conduction studies. Patients satisfying the inclusion criteria were randomly assigned to receive Axsain cream (n=138) or vehicle cream (n=139). Pain assessments were performed using both categorical and visual analogue scales at baseline, two, four, six, and eight weeks. The study was conducted in accordance with good clinical practice.

Efficacy determinations were based on results from 252 patients who used Axsain for two weeks or more and participated in at least one evaluation during the treatment period.

The results of Study #88-17 are presented in Table 4. In the Physician's Global Evaluation, there were significantly more improved patients in the Axsain-treated group when compared to the vehicle group at each time period. By the end of the study, 71.3% of the Axsain-treated patients reported some degree of pain relief. Most of the patients who experienced improvement over the course of the study reported amelioration of pain during the initial two weeks of treatment (56.5%). Thereafter, the percentage of improved patients receiving Axsain increased by 14.8% from Week 2 to Week 8 of the study compared to 8.3% for the vehicle-treated group.

Table 4: Results of 88-17

Percentage Improvement from Baseline								
	Weeks							
	2		**4**		**6**		**8**	
	C (117)	V (128)	C (110)	V (124)	C (100)	V (117)	C (94)	V (111)
Physician's global evaluation scale (% improved patients)	56.5	43.0	69.1	54.8	74.0	58.1	71.3	51.3
	p = 0.042		p = 0.045		p = 0.017		p = 0.007	
VAS-pain severity (% reduction)	16.6	13.7	29.5	25.1	38.3	29.4	40.1	27.8
	p = 0.438		p = 0.307		p = 0.071		p = 0.014	
VAS-pain relief (% relief)	35.4	31.0	50.0	40.8	58.1	45.3	59.5	45.4
	p = 0.228		p = 0.031		p = 0.004		p = 0.005	

C = capsaicin 0.075% cream; V = vehicle cream; (number of subjects)

Patients in the Axsain-treated group also demonstrated a greater reduction of pain using both the VAS for Pain Severity and the VAS for Pain Relief. The degree of pain relief on the VAS-Pain Relief scale was significantly greater in the capsaicin-treated group at four weeks (p=0.031), six weeks (p=0.004) and eight weeks (p=0.005), and the reduction in pain intensity on the VAS-Pain Severity scale was significantly greater in the capsaicin-treated group at Week 8 (p= 0.014).

Pain measurements were also analyzed for differences between Axsain-treated patients and the vehicle group at the final visit. This was accomplished by pooling data from patients who withdrew prematurely from the study (but had at least one treatment evaluation) with results of patients who completed the entire study (See Table 5). Final visit analyses of efficacy measures revealed a significant improvement favouring the capsaicin-treated group for Physician's Global Evaluation, VAS-Pain Severity, and VAS-Pain Relief.

Table 5

Final Visit Analyses of Efficacy Measures			
	Capsaicin	**Vehicle**	**P-Value**
Physician's Global Evaluation, % of patients improved (n)	69.5 (121)	53.4 (131)	0.012
VAS-Pain Severity, % improvement from baseline (n)	38.1 (119)	27.4 (131)	0.037
VAS-Pain Relief, % relief from baseline, (n)	58.4 (120)	45.3 (131)	0.004

The results of Study #88-17 clearly demonstrate that Axsain cream is effective treatment for managing the pain associated with diabetic neuropathy. At the end of the study, over 70% of the patients treated with capsaicin reported pain relief; pain was reduced by an average of nearly 60%. Significant effects were observed after two weeks of capsaicin application with progressive improvement for the remainder of the trial; no tolerance to the analgesic effects of topical capsaicin was observed.

The effect of pain relief produced by capsaicin treatment on a patient's quality of life was also determined in Study #88-17 (also see Dailey *et al* [45]). Categorical Functional Capacity Scales were used to rate the interference of pain with the following daily activities: working, sleeping, walking, participating in recreational activities, wearing shoes and socks, and eating. Results are presented in Table 6.

Table 6

Functional Capacity at the Final Visit: Mean Percentage Improvement from Baseline			
	Capsaicin	Vehicle	P-value
Recreation	22.8 (n=105)	12.1 (n=108)	p = 0.037
Working	18.3 (n=114)	9.2 (n=121)	p = 0.019
Wearing shoes & socks	12.5 (n=118)	10.7 (n=127)	p = 0.832
Walking	26.1 (n=129)	14.6 (n=119)	p = 0.029
Eating	2.5 (n=120)	0.6 (n=121)	p = 0.642
Sleeping	29.5 (n=120)	20.3 (n=131)	p = 0.036

Patients in the Axsain-treated group showed significantly greater improvement in their ability to work, sleep, walk, and participate in recreational activities than those in the vehicle group. Painful diabetic neuropathy caused little or no interference with eating at baseline and eating was not affected by either treatment during the study. There was a tendency for improvement in wearing shoes and socks with capsaicin treatment, but there were no significant differences between the groups at any point in the study.

Overall, the results point to an association between the pain-relief that patients experienced with Axsain and a noticeable improvement in quality of life. The effects on sleep are particularly noteworthy since a large percentage of patients were having difficulties sleeping prior to the study.

Several of the research groups involved in the 277-patient multicentre trial, reported separately on their cohort of patients (35,47-49). The reports of Tandan *et al* (35,48) are of interest as they provide additional information not reported by Donofrio *et al* (44) or Dailey *et al* (45). A description of Axsain treatment on sensory perception can be found in the Clinical Pharmacology section of this report (page 9).

At the conclusion of the eight-week double blind period, Tandan *et al* (48) investigated the long-term effects of capsaicin in eighteen subjects (vehicle-treated and capsaicin-treated) who were given the option of participating in an open label investigation. The subjects were evaluated at two and eight weeks after entry and every eight weeks thereafter for a total of 48 weeks.

When compared to the final double-blind treatment visit, approximately 50% of the patients were improved, 25% were unchanged, and 25% experienced worsening pain.

Study #89-02: This multicentre study was conducted in 235 patients with painful distal symmetrical polyneuropathy. Patients were randomly assigned to two treatment groups; 1) Axsain cream (0.075%), four times daily and placebo capsules, or 2) a topical vehicle cream with amitriptyline beginning at 25mg and then force-dose titrated to a maximum of 125mg over a period of eight weeks. Following the eight-week, double-blind period, patients received both Axsain and amitriptyline (maximum tolerated dose up to 125mg) in a single-blind fashion for a period of four weeks. One hundred seventy-nine patients completed the eight-week double-blind phase of the study and 155 completed the entire study.

Patients had to discontinue amitroptyline or any other tricyclic antidepressant at least seven days prior to the start of the study. Patients who were receiving other oral analgesic medications for painful diabetic neuropathy or receiving drug therapy for any other conditions were allowed to continue these medications without change in dosage or frequency of administration throughout the study.

In order to protect the blinded nature of this study which involved two drugs with different dosage forms, each with a distinctly different adverse effect profile, agents that mimic the adverse effects of the active drugs were incorporated into the placebo capsule and vehicle cream. Methyl nicotinate was selected as agent mimicking the adverse effects of capsaicin and was placed only in the first tube of vehicle cream distributed to each patient assigned to receive amitriptyline capsules. All tubes previously dispensed were collected at the subsequent visit, and the tube of vehicle cream with methyl nicotinate was not used beyond the first two weeks of Phase I.

Two agents were chosen to be incorporated in the placebo capsules designed to mimic the adverse effects of amitriptyline. Diazepam was used because of its CNS effects, e.g., sedation, and benztropine was used because of its anticholinergic effects, e.g., dry mouth. All patients assigned to Axsain treatment group during Phase I received placebo control capsules containing the mimicking agents. For the first three days, a dose of 0.25 mg benztropine and 2 mg diazepam was incorporated into each placebo capsule followed by four days of 0.50 mg benzatropine and 4 mg of diazepam. If the patients were able to tolerate this dosing, they were given 0.75 mg benztropine and 6 mg diazepam on a daily basis during the second week of treatment. Beginning in the third week, the daily dose of benztropine was increased to 1.0 mg when tolerated, but the diazepam was discontinued. The maximum possible exposure to benztropine was 1.25 mg per day.

Categorical and visual analogue scales were used to assess pain intensity, pain relief, and the ability to conduct daily activities. The Physician's Global Evaluation was designated apriori as the primary determination of efficacy. Assessments were conducted at baseline and then again following 2, 4, 6, 8, 10, 12 and 14 weeks of double-blind treatment. Table 7 summarizes the Categorical Verbal Intensity Scores for pretreatment pain (baseline) by treatment group for each type of pain described by the patients. Burning pain was the most frequently reported type of pain occurring in 77.4% of the patients enrolled in the study.

Table 7: Categorical Verbal Intensity Scores for Baseline Pain

PAIN TYPE	N	SLIGHT	MODERATE	SEVERE	VERY SEVERE	BETWEEN GROUP P-VALUE
ACHING						
Capsaicin	80	5 (6%)	37 (46%)	31 (39%)	7 (9%)	0.06
Amitriptyline	88	3 (3%)	36 (41%)	35 (40%)	14 (16%)	
BURNING						
Capsaicin	98	6 (6%)	38 (38%)	43 (43%)	11 (11%)	0.90
Amitriptyline	84	8 (10%)	28 (33%)	37 (44%)	11 (13%)	
CRAMPING						
Capsaicin	49	10 (20%)	16 (32%)	18 (37%)	5 (10%)	0.21
Amitriptyline	62	6 (10%)	24 (39%)	25 (40%)	7 (11%)	
STINGING						
Capsaicin	74	9 (12%)	34 (46%)	23 (31%)	8 (11%)	0.06
Amitriptyline	76	4 (5%)	33 (43%)	29 (38%)	10 (13%)	
THROBBING						
Capsaicin	52	7 (13%)	29 (56%)	11 (21%)	5 (10%)	0.14
Amitriptyline	50	4 (8%)	21 (42%)	16 (32%)	9 (18%)	
STABBING						
Capsaicin	73	4 (5%)	15 (21%)	33 (45%)	21 (29%)	0.76
Amitriptyline	79	4 (5%)	16 (20%)	37 (47%)	22 (28%)	

The Physician's Global Evaluation results are summarised in Table 8. Favourable responses to both drugs were evident by the second week of treatment, and by the end of Week 8 over 75% of the patients in each treatment group showed at least some improvement. Over 85% of the patients in both groups reported pain relief by the end of Week 14. No statistically significant differences between the capsaicin and amitriptyline treatment groups were detected at the final visit for Phase I (73% versus 73%, respectively), nor at the final visit for Phase II (87% versus 84%, respectively). The only significant differences between treatment groups were observed at Weeks 10 and 12, and were attributable to the more rapid onset of action of amitriptyline when added to baseline capsaicin therapy as compared to the slower onset of action of capsaicin when added to amitriptyline therapy.

Table 8: Physician's Global Evaluation

	N	Much Worse	Worse	No Change from baseline	Better	Much Better	Completely Gone	% of total patients improved	Between Group P-Value
Capsaicin (n=118) - Percent of Patients									
WK2	104	2%	3%	23%	48%	20%	4%	72%	.60
WK4	96	1%	4%	19%	41%	29%	6%	76%	.68
WK6	93	0	6%	18%	34%	34%	6%	74%	.87
WK8	92	0	4%	21%	38%	29%	9%	76%	.90
Final Visit	104	2%	4%	22%	35%	30%	8%	73%	.91
WK10	89	0	3%	9%	27%	46%	15%	88%	.04
WK12	84	0	2%	11%	13%	52%	21%	86%	.04
WK14	83	0	1%	12%	14%	48%	24%	86%	.17
Final Visit	89	0	1%	11%	16%	49%	22%	87%	.053
Amitriptyline (n=117) - Percent of Patients									
WK2	108	1%	0	23%	52%	20%	4%	76%	
WK4	95	0	2%	15%	46%	46%	5%	83%	
WK6	91	1%	7%	14%	36%	35%	7%	78%	
WK8	87	1%	5%	29%	29%	36%	11%	76%	
Final Visit	108	1%	5%	21%	31%	32%	10%	73%	
WK10	82	0	10%	16%	23%	38%	13%	74%	
WK12	75	1%	5%	11%	29%	39%	15%	83%	
WK14	72	1%	3%	10%	29%	35%	22%	86%	
Final Visit	82	2%	2%	11%	30%	32%	22%	84%	

The mean changes in VAS-Pain Severity scores from baseline are presented in Table 9 for each treatment group at the final visit during each study phase. Changes are calculated as the final value subtracted from the baseline visit value. Changes with negative values indicate decreased pain. The changes within each group from baseline to the final visit were significant. No statistically significant differences between the treatment groups was noted.

Table 9: Mean Changes in VAS - Pain Severity Scores

	n	Mean* Baseline	Mean* Change in VAS-pain (± SEM)	Mean* Percent Change in VAS-pain	P-Value	
					Within group	Between group
Phase I final visit:		(Wk. 0)				
Capsaicin	104	62.1	-26.1 ± 2.9	-42.0	< 0.01	0.40
Amitriptyline	108	66.5	-29.1 ± 3.0	-43.8	< 0.01	
Phase II final visit:		(Wk. 0)				
Capsaicin	88	60.7	-41.7 ± 3.2	-68.7	< 0.01	0.79
Amitriptyline	81	56.9	-40.6 ± 3.4	-60.7	< 0.01	

* Least square mean.

The mean values of VAS-pain relief for both treatment groups are shown in Table 10.

Patients in both treatment groups in both phases improved significantly ($p<0.01$). No significant differences between treatment groups were noted.

Table 10: VAS Pain Relief Scores

	n	Mean* VAS-pain relief (± SEM)	P-Value	
			Within Group	Between Group
Phase I final visit:				
Capsaicin	104	55.1 ± 3.5	< 0.01	.66
Amitriptyline	108	57.0 ± 3.6	< 0.01	
Phase II final visit:				
Capsaicin	89	78.0 ± 3.6	< 0.01	.11
Amitriptyline	81	70.8 ± 3.7	< 0.01	

* Least square mean

The effect of capsaicin or amitriptyline treatment alone (Phase I) or combined therapy (Phase II) on the ability to conduct daily activities as determined at the final visit is reported in Table 11. The most impaired activity at baseline was sleeping. Both treatments produced substantial improvement at the Phase I final visit. Significant improvement in walking, driving, home chores, wearing shoes, and recreation were also observed with either treatment. A significant effect on eating was detected only

in the Axsain-treated group at the final visit and working was significantly improved only in the amitriptyline group. These results were generally reflective of more consistent improvements across all time points for Axsain treatment and improvements in eating and for amitriptyline treatment and improvements in working. Except for working, there was no statistically significant difference between treatment groups during Phase I. During Phase II, consistent improvement in daily activities was limited to sleeping. Wearing shoes, walking, and driving were significantly improved in patients who received capsaicin in Phase I with amitriptyline added in Phase II. Except for sleeping, no changes were observed at the final Phase II visit in patients receiving amitriptyline in phase I with Axsain added in Phase II.

Table 11: Effect of Daily Activities

	Percent change from baseline			
	Phase I		Phase II	
	Baseline Score	Final visit: % change from baseline*	Baseline Score (Week 8 - Phase 1)	Final visit: % change from baseline*
Eating:				
Capsaicin	0.15, n=118	-66.7 (0.02); n=103	0.06, n=103	20.0 (0.66); n=89
Amitriptyline	0.16, n=116	-29.4 (0.25); n=107	0.07, n=107	-33.3 (0.42); n=81
Sleeping:				
Capsaicin	2.01, n=118	-56.7 (0.001); n=103	0.82, n=103	-40.3 (0.001);n=89
Amitriptyline	2.03, n=117	-58.8 (0.001); n=108	0.78, n=108	-26.2 (0.043);n=82
Wearing shoes:				
Capsaicin	1.36, n=118	-34.0 (0.001); n=103	0.89, n=103	-30.4 (0.006);n=89
Amitriptyline	1.18, n=117	-50.4 (0.001); n=108	0.59, n=108	4.0 (0.84); n=82
Walking:				
Capsaicin	1.76, n=115	-23.3 (0.001); n=100	1.26, n=100	-22.2 (0.012);n=87
Amitriptyline	1.68, n=117	-36.7 (0.001); n=107	0.92, n=107	-11.8 (0.26);n=82
Driving:				
Capsaicin	0.66, n=104	-50.0 (0.001); n=87	0.29, n=87	-30.0 (0.013);n=75
Amitriptyline	0.84, n=99	-41.1 (0.001); n=88	0.53, n=88	0 (0.95);n=69
Home chores:				
Capsaicin	1.07, n=104	-36.0 (0.001); n=85	0.60, n=85	-16.6 (0.18);n=74
Amitriptyline	1.17, n=109	-40.2 (0.001); n=91	0.59, n=91	- 7.7 (0.62);n=67
Recreation:				
Capsaicin	1.31, n=88	-20.0 (0.033); n=64	0.76, n=64	- 9.8 (0.42);n=58
Amitriptyline	1.38, n=88	-27.3 (0.003); n=72	0.69, n=72	-23.5 (0.2); n=50
Working:				
Capsaicin	0.93, n=61	-28.9 (0.078); n=50	0.51, n=50	-26.3 (0.2); n=43
Amitriptyline	1.13, n=54	-48.6 (0.003); n=40	0.51, n=40	- 5.3 (0.82); n=31

* Within treatment group P-values in parenthesis

These data are compatible with the findings of Study #88-17 (Donofrio *et al* [44]) for capsaicin (0.075%) and for amitriptyline reported by Max *et al* (50). Phase II of the study recorded further gains in clinical improvement when Axsain and amitriptyline were used concomitantly. Treatment of painful diabetic neuropathy with topically applied Axsain cream appears to have an efficacy profile comparable to amitriptyline. The results suggest that capsaicin can be used alone or in combination with amitriptyline to provide symptomatic relief of pain associated with diabetic neuropathy.

Study of **Pfeifer *et al* (46)**

In a controlled case series, Pfeiffer *et al* (46) categorised patients with distal symmetrical polyneuropathy according to whether they were experiencing superficial,

muscular, and/or deep pain and then treated them with Capsaicin (0.75%); stretching alone or with metaxalone ± piroxicam; or imipramine ± mexiletine; respectively. Twenty-two patients volunteered to remain untreated and 53 patients were treated for a period of three months.

Pain was characterized using a graphic rating scale. Pain for each source (superficial, muscular, deep) was scored separately by the patient using this graphic rating scale 0 (no pain) to 19 (worse pain imaginable). Patients were asked to grade burning sensations, allodynia for superficial pain; "pins and needles", electric-like pain, and numbing/aching for deep pain; deep aches, toothache-like pain, spasms, and cramps were scored as muscular pain. A specific type of pain was considered to be present if a patient scored that type of pain with a score of ≥3. The total of all three components was used as an overall index of pain. Sleep was evaluated on a five-point scale and based on the patient's ability to sleep through the night (1, never; 2 seldom; 3, sometimes; 4, usually; 5, always). A comprehensive neurological examination was performed on all patients.

Patients most commonly complained of all three types of pain (treated group = 75.5%; untreated group = 77.3%) and seldom had a single type of pain as their presenting symptom (treated group = 5.7%, untreated group = 4.5%). Two types of pain were occasionally seen (treated group = 18.9%, untreated group = 18.2%). In the treatment group, the initial total pain score was composed of 25±2% superficial pain, 38±3% deep pain and 37±3% muscular pain.

All fifty patients reporting superficial pain were treated with capsaicin. None of the patients were unable to tolerate capsaicin. Patients reporting a superficial (dysesthetic) type of pain (burning, allodynia, and tingling) were started on capsaicin cream (0.075%) applied four times daily. Patients reporting pain from deeper anatomical sites characterized as "pins and needles" or electric-like were treated with imipramine (50-150 mg per day). When imipramine was either not tolerated or did not provide adequate pain relief, drug treatment with mexiletine was initiated (10 mg/kg/day divided into three or four equal doses). Muscular pain was treated by stretching exercises and a skeletal muscle relaxant, metaxalone (800 mg tid or qid). If insufficient improvement was observed, piroxicam (20 mg qd) was added.

The responses to therapy are listed in Table 12. After three months, the total pain score and each of the individual pain scores were significantly decreased in the treated group whereas the scores of the untreated group were statistically unchanged. Moreover, the change in the pain score was significantly improved relative to the untreated group. Sleep showed similar improvement.

Table 12: Responses to Therapy

	Treated Group (n=53)			Untreated Group (n=22)			Between group P value**
	Initial Score	Final Score	P value*	Initial Score	Final Score	P value*	
Superficial pain	8.0±0.8	2.8±0.4	0.0001	9.0±1.4	8.5±1.4	NS	0.0001
Deep pain	10.5±0.8	3.7±0.5	0.0001	11.9±1.1	12.1±1.3	NS	0.0001
Muscular pain	9.9±0.7	3.6±0.5	0.0001	11.0±1.2	10.7±1.4	NS	0.0001
Total pain	28.4±1.7	10.0±1.3	0.0001	32.0±3.1	31.3±3.4	NS	0.0001
Sleep	2.3±1.1	3.5±0.1	0.0001	2.2±0.3	2.5±0.3	NS	0.0001

Data are mean ± SEM;

* Calculated with paired Student's T test; initial vs final score.
** Calculated with independent Student's T test; changes in scores of treated vs untreated group.

Correlates to improvement in pain symptoms were determined in the treated group by stepwise regression analysis using the following baseline variables: gender, duration of diabetes, age, BMI, glycosylated hemoglobin, log of duration of neuropathy, toe thermal perception threshold, toe vibratory perception threshold, peroneal and sural nerve conduction velocities, type of diabetes, treatment of diabetes, and level of hyperaesthesia during pinprick exam. None of the variables were significantly related to the change in superficial or total pain scores. The change in the muscular pain score was related to the initial level of hyperaesthesia, the log of the monofilament determination, and gender ($p<0.05$). The change in the deep pain score was significantly related to the duration of diabetes and the log duration of the neuropathy ($p<0.01$).

Although the results of this study need to be confirmed in a placebo-controlled, double-blind trial, the study of Pfeifer and associates (46) presents an intriguing algorithm for the successful treatment of painful diabetic neuropathy. It uniquely bases the treatment algorithm on the types of pain that are being experienced. Capsaicin cream (0.075%) plays a central role in thisapproach to treating pain diabetic neuropathy.

3.2. Global Analysis of Efficacy

Reports of four clinical trials are included in this review, three of which were double-blind, randomized studies. Two studies were comparative against placebo, one study was comparative against amitriptyline, and the fourth was an open-label investigation. In addition, a subset of patients from one of the placebo controlled trials was evaluated in a long-term, open-label, non-comparative phase immediately following the double-blind phase. A total of 570 patients aged 21-92 years were randomized in these trials; 440 patients completed the double-blind component of the studies. Of the 285 patients randomized to receive Axsain alone, 216 completed this component of the studies. One hundred seventy-nine patients received combination therapy of

Axsain and amitriptyline in a single-blind analysis; 155 completed all study visits. All subjects had stable diabetes mellitus Type I or II with associated painful neuropathy confirmed by symptoms and neurological examination. Fifty patients received Axsain alone or in combination with imipramine and/or mexiletine, stretching exercise, metaxalone, piroxicam for a three month period in an open-label study. All fifty patients continued to use Axsain for the duration of the study.

The pivotal efficacy and safety studies evaluating Axsain cream in painful diabetic neuropathy employed both categorical rating scales and visual analogue scales to determine the degree of pain relief. Both techniques are commonly used in pain studies and are well accepted by experts in the study of pain. In the case of clinical rating scales, impressions of either the investigator or the patient are recorded on a 4 to 6 point categorical scale that are subsequently given a numerical value. The visual analogue scale (VAS) provides a nonclassical measure of pain intensity. It has been reported to be sensitive to both pharmacological and nonpharmacological procedures which alter the degree of pain. One major advantage of the VAS as a measure of pain is its ratio scale properties. In contrast to many other measurements of pain, equality of ratios is implied with this technique allowing it to be used in an meaningful fashion when discussing multiple time points or independent samples of subjects (51).

Common statistical methodology was employed. Demographic equivalency among groups was determined either by the Chi Square Test, Student's T-test, or Fischer's Exact Test depending on the variable analyzed. Generalized Cochran-Mantel-Haenszel statistics based on rank scores were used to evaluate variables with discrete scales. VAS data were analyzed by analysis of variance adjusted for each investigator using the method of least mean squares. Log transformations were used to normalize data. Other methods used included paired T-tests, stepwise regression and McNemar's test of correlated proportions.

Table 13 provides an abbreviated summary of the efficacy of Axsain cream.

Studies #88-17 & #89-02 demonstrated significant pain relief using both the VAS determinations and the Physician's Global Evaluation in conjunction with quality of life improvements either versus placebo (#88-17) or when compared to predrug conditions (#89-02). In addition, Axsain provided pain relief equal to amitriptyline in a large double-blind, controlled trial. These are significant findings given that tricyclic antidepressants are generally recognized as first line analgesic therapy for the management of pain associated with diabetic neuropathy. Insufficient sample size and short study duration more than likely played a large role in the lack of statistically significant changes observed in Study #87-01 especially in light of the fact that the apparent capsaicin-induced effects in this study were comparable in magnitude to the two other larger eight-week trials. When taken together, the evidence strongly suggests that Axsain is effective in managing the pain associated with diabetic neuropathy. The efficacy of Axsain is comparable to tricyclic antidepressants and of sufficient magnitude to improve a patient's quality of life.

Minimal data are available to analyze the long-term (beyond eight weeks) efficacy and safety of Axsain in painful diabetic neuropathy. In the small number of subjects (n=17) followed in an uncontrolled manner, 75% were improved or had the same pain relief when compared to the conclusion of the double-blind treatment period (48).

Other long-term experience with capsaicin (0.075%) has been reported from an uncontrolled trial of 83 patients with postherpetic neuralgia (52). Patients participated in a six week, double-blind study followed by continuing open-label drug treatment for a mean of 140 additional days (range 43-708 days). When compared to the end of the six week double-blind treatment period, 86% of the patients were maintained or improved. These studies demonstrate that tolerance does not develop to the analgesic action of capsaicin (0.075%).

Table 13: Summary of the Efficacy of Axsain

	Study #87-01	Study #88-17	Study #89-02
Number of patients enrolled	58	277	235
Number of patients completing the study	46	219	179
Medications	0.075% capsaicin; 4 times daily vs placebo	0.075% capsaicin; 4 times daily vs placebo	0.075% capsaicin; 4 times daily vs amitriptyline (25-125 mg)
Length of the study	four weeks	eight weeks	eight weeks
Patients withdrawing from drug treatment due to lack of efficacy	not reported	none	one patient
Physician's Global Evaluation - % patients improved at the end of trial vs (placebo) or [amitriptyline]	71 vs. (50)	71.3* vs. (51.3)	76 vs. [76]
VAS-Pain Severity - % improvement at end of trial vs (placebo) or [amitriptyline]	38 vs. (20)	40.1* vs. (27.8)	42.0** vs. [43.8]**
VAS-Pain Relief - % relief at end of trial vs (placebo) or [amitriptyline]	45 vs (31)	59.5* vs. (45.4)	55.1** vs. [57.0]**

* $p<0.05$ vs placebo; ** $p<0.01$ vs baseline at final visit

3.3. Global Analysis of Safety

The most common adverse reactions reported by patients treated with Axsain in Studies 87-01, 88-17, & 89-02 are listed in Table 14.

Table 14: Summary of Most Common Adverse Reaction

	Study #87-01	Study #88-17	Study #89-02
Number of patients enrolled; capsaicin vs. (vehicle) or [amitriptyline]	29 (29)	138 (139)	118 [117]
Total number of adverse effects reported vs. (vehicle) or [amitriptyline]	7 (5)	135 (49)	89 [83]
Percentage of patients reporting burning pain with application vs. (vehicle) or [amitriptyline]	12.5 (13.6)	63.0 (16.5)	44.1 [0]
Percentage of patients reporting coughing/ sneezing vs (vehicle) or [amitriptyline]	0 (0)	11.6 (1.4)	6.0 [0]
Percentage of patients reporting rash/erythema/ warmth vs. (vehicle) or [amitriptyline]	0 (0)	7.2 (2.9)	5.1 [0]
Percentage of patients reporting pruritus vs. (vehicle) or [amitriptyline]	0 (4.5)	not reported	6.8 [1.7]
Percentage of patients reporting exposure/ irritation to other parts of body	6.5 (0.7)	6.5 (0.7)	not reported
Percentage of patients with increased pain	4.2 (0)	1.4 (3.6)	not reported

Topically applied capsaicin is known to have an initial excitatory effect on small unmyelinated nociceptive C-fibres leading to sensations of warmth, stinging, and burning. In healthy volunteers Simone and Ochoa (34) reported that each application of Axsain evoked mild burning pain in all subjects, usually lasting 30-60 minutes.

With repeated applications this adverse sensation decreased in both magnitude and duration but nonetheless, was still being reported after five weeks of treatment. Axsain did not produce any visible flare.

Of the 46 patients with painful diabetic neuropathy in Study #87-01, four patients in each treatment group were reported by the authors as experiencing adverse effects related to treatment. In the Axsain-treated group one patient each experienced mild, moderate, and severe burning pain of the feet after application. The case of mild burning resolved spontaneously after one week; the individual with moderate pain burning responded to reducing the amount of medication applied but the burning sensation persisted for the duration of the study; the severe burning, restricted to the dorsal surfaces of the feet, subsided in one day when application to these areas was omitted. The fourth Axsain-treated patient experienced intensification of pain in the feet which was controlled by discontinuing the medication for two days and adding an oral analgesic agent. In the vehicle-treated group, two patients experienced mild burning and one patient severe burning of the feet after application. A fourth Axsain-treated patient complained of moderately severe pruritus in treated skin areas. The mild burning was transitory and required no specific intervention. The severe burning lasted for the duration of the study. The pruritus lasted for ten days and then subsided spontaneously.

Table 15 lists those adverse effects reported in Study #88-17. Adverse effects reported most frequently in this study included burning pain following application, coughing sneezing, exposure/irritation to non-treated areas of the body, and rash/erythema. No systemic adverse effects attributable to study medication were observed in either group. Burning pain was the most frequent adverse effect in both groups; it was reported by 63% of capsaicin-treated patients and 17% of the patients in the vehicle group. By the end of the study, only 34 of 87 (39%) capsaicin-treated patients initially reporting burning pain continued to experience any burning, suggesting that this effect becomes more tolerable or ceases to exist with continued use. Coughing and sneezing were more prevalent in the capsaicin-treated patients and were postulated to be due to excessive application of the cream resulting in, "caking" of the dried capsaicin residue on the skin with subsequent aerosol formation and inhalation.

Table 15: Adverse Effects Reported in Study 88-17

	Capsaicin Group (n=138)	Vehicle Group (n=139)
Total reports	135	49
Burning	87	23
Coughing/sneezing	16	2
Exposure/irritation to other parts of the body	9	1
Rash/erythema	10	4
Dry skin	5	6
Increased pain	2	5
Other	6	8

Eighteen patients in the Axsain-treated group and five patients in the vehicle group withdrew from the study because of adverse effects. In the Axsain-treated group, 14 patients discontinued treatment due to burning pain associated with application, 11 of these patients withdrew during the first two weeks of treatment. Two patients from the vehicle group discontinued the study prematurely due to burning pain associated with application of the cream. One patient from each treatment group withdrew from the study due to intensification of pain or due to rash/erythema.

Adverse effects reported from the Study #89-02 are listed in Table 16. To compare the safety experience of capsaicin and amitriptyline, adverse effects attributed to the agents used to mimic their respective adverse effects, i.e., the topical drug for patients assigned to receive amitriptyline and the oral drug for patients assigned to receive capsaicin, or adverse effects unrelated to any drug were excluded. All adverse effects related to capsaicin were at the site of application. Forty-four percent of the patients receiving capsaicin experienced a burning sensation. A wide range of adverse effects were reported by patients receiving amitriptyline; the most frequently reported were somnolence (46%), dry mouth (33%), dizziness (9%), and constipation (9%).

Table 16: Adverse Effects Reported in Study 89-02

	Capsaicin (n=118)	Amitriptyline (n=117)
Gastrointestinal		
Constipation	0	10
Dyspepsia	0	4
Anticholinergic		
Abnormal vision	0	1
Amblyopia	0	1
Dry mouth	0	39
Impotence	0	1
Urinary retention	0	4
Dysuria	0	1
CNS-Neuromuscular		
Abnormal dreams	0	2
Anxiety	0	3
Confusion	0	6
Depression	0	1
Emotional liability	0	1
Hallucinations	0	1
Headache	0	2
Hypokinesia	0	1
Insomnia	0	1
Libido decreased	0	1
Migraine	0	1
Nervousness	0	1
Paresthesia	0	1
Speech disorder	0	2
Thinking abnormal	0	1
Tinnitus	0	1
Tremor	0	1
Cardiovascular		
Bundle branch block	0	1
Chest pain	0	1
Hypertension	0	1
Palpitation	0	3
Postural hypotension	0	1
Tachycardia	0	1
Edema	1	2

Table 16: Adverse Effects Reported in Study 89-02 cont...

	Capsaicin (n=118)	Amitriptyline (n=117)
Sedative		
Asthenia	0	4
Dizziness	0	10
Hangover	0	1
Somnolence	0	54
Skin: Application Site		
Burning/tingling	52	0
Pruritus	8	2
Erythema/warmth	5	0
Rash	1	0
Blister	1	0
Miscellaneous		
Coughing/sneezing	7	0
Sweating	0	1

The pattern and incidence rate of adverse effects reported in Phase II of the study are listed in Table 17. The most common adverse effect attributed to capsaicin was a burning sensation at the site of application (58%). The most frequently reported adverse effects attributed to amitriptyline were somnolence (66%) and dry mouth (60%).

Table 17: Adverse Effects in Phase II of Study 89-02

Drug Assignment in Phase I: Drug that Adverse Effect was attributed to in Phase II:	Amitriptyline Capsaicin (n=89)	Capsaicin Amitriptyline (n=83)
Gastrointestinal		
Constipation	0	8
Dyspepsia	0	5
Nausea	0	2
Anticholinergic		
Dry mouth	0	50
Impotence	0	1
Urinary retention	0	5
Dysuria	0	1
CNS-Neuromuscular		
Abnormal dreams	0	1
Amnesia	0	1
Confusion	0	4
Depression	0	1
Headache	0	2
Nervousness	0	2
Tremor	0	1
Tardive dyskinesia	0	1
Cardiovascular		
Palpitation	0	1
Edema	2	0
Sedative		
Asthenia	0	9
Dizziness	0	5
Somnolence	0	55
Skin: Application Site		
Burning/tingling	52	1
Pruritus	8	0
Erythema/warmth	8	0
Rash	1	0
Miscellaneous		
Cold/flu/allergy	0	1
Cough/sneezing	2	0
Taste perversion	0	3

Adverse effects associated with premature withdrawal from the Study #89-02 are listed in Table 18. Some patients listed more than one adverse experience as the reason for withdrawal from the study. Also, the results indicate that some patients in both treatment groups withdrew from Phase I of the study because of adverse effects produced by the "mimicking" drugs. For example, five patients receiving capsaicin therapy discontinued the study as a result of somnolence.

Table 18: Adverse Effects Associated with Premature Withdrawal from Study 89-02

	PHASE I		PHASE II
	Capsaicin (n=19)	Amitriptyline (n=14)	Capsaicin and Amitriptyline (n=7)
Burning	18	3	5
Somnolence	5	7	0
Dry mouth	1	1	2
Anxiety	1	0	0
Dizziness	1	1	0
Confusion	1	3	0
Abnormal	0	1	0
Erythema	0	1	1
Pruritus	0	3	0
Blistering	0	1	0
Asthenia	0	1	1
Palpitation	0	2	0
Edema	0	1	0
Constipation	0	1	0
Glossitis	0	0	1
Rash	0	1	1

Over the course of the 14-week study, reports of a burning sensation following Axsain application progressively decreased. Less than 45% of the patients experiencing this adverse effect at the beginning of the trial were experiencing a burning sensation after 14 weeks (Axsain-treated patients, Phase I). An increase in the incidence of burning pain with application on Week 10 in the group receiving amitriptyline in Phase I reflects the introduction of Axsain cream. After four weeks of treatment the incidence of burning pain with application greatly diminished in this group as well.

4. POST-MARKETING EXPERIENCE

No serious unexpected adverse events have been reported in the U.S. with capsaicin (0.025%) since the product was introduced in 1987 (approximately 3 million tubes sold). The 2-year post-marketing experience with capsaicin (0.075%) is similar. The most common adverse effect that has been reported with the use of either capsaicin 0.025% or 0.075% is stinging or burning pain at the application site. Erythema and/or rash have been infrequently reported in post-marketing surveillance of capsaicin - approximately 1 incident reported by consumers per 100,000 units sold. On rare occasions, there have been reports that capsaicin 0.025% or 0.075% was associated with a respiratory irritant effect resulting in coughing, sneezing, rhinitis, and/or difficulty breathing. In some instances these conditions have required treatment. Usually, this type of event is the result of over-application of the cream and/or a failure to wash off previous applications before reapplying. As a result, the dried capsaicin becomes airborne and is inhaled. Overall, the U.S. post-marketing experience supports the contention that capsaicin 0.025% or 0.075% are extremely safe products.

5. CONCLUSIONS

5.1. Therapeutic Justification

Painful diabetic neuropathy is a widespread disorder that will eventually affect a large percentage of those individuals with diabetes mellitus. Painful diabetic neuropathy has proven to be a difficult condition to treat with relatively few patients achieving satisfactory pain relief. Patients are often traumatized by their pain and are desperate for relief; many suffer from insomnia in conjunction with an inability to carry out daily activities. Anxiety and depression are also common concurrent conditions. The physician faces a dilemma in the treatment these patients. The drugs that are available often lack the necessary efficacy, cause adverse effects that cannot be tolerated, interact with other required drugs the patient may be taking, or are potentially addictive. In short, the physician does not have access to a therapeutic modality that is routinely both safe and effective. There is little doubt that options for better drug therapy are desperately needed to manage the pain of diabetic neuropathy.

Selectivity of pharmacological action is the feature that distinguishes Axsain from all drug therapy currently used to manage neuropathic pain. It is the only drug that provides pain relief for neuropathic pain by specifically interfering with the activity of damaged or dysfunctional polymodal C-fibres. Therefore, unlike the systemic medications that are commonly employed to manage painful diabetic neuropathy such as tricyclic antidepressants and anticonvulsants, Axsain selectively affects pain transmission and does not affect normal CNS functions. Equally important, topical capsaicin therapy does not interfere with the perception of other sensations (touch, vibration, etc.) from the treated area which may already be impaired in the diabetic patient.

5.2. Efficacy

Axsain cream has been shown to be a novel and effective preparation for the management of the pain associated with diabetic neuropathy with an efficacy profile similar to amitriptyline. The results of several multicentre, well-controlled clinical trials demonstrate that Axsain provides significant pain relief to a majority of patients with established diabetic neuropathy. Moreover, the magnitude of pain relief translated to a clear clinical benefit. Patients treated with Axsain were able to increase their productivity, mobility, ability to sleep, such that their quality of life was significantly improved.

5.3. Safety

Axsain cream poses minimal risk of serious systemic adverse effects to the patient with painful diabetic neuropathy. This characteristic is impressive when contrasted to other pharmacological approaches used to manage painful diabetic neuropathy which expose the patient to a wide range of adverse effects, some potentially serious or life-threatening. The risk of adverse effects takes on an added measure of importance in the diabetic patient, whose health and general well-being may already be compromised by diabetes and/or any one of many long-term complications associated with the disease.

Pre-existing neurophysiological impairment in patients with diabetic neuropathy places them at risk of further adverse consequences. To be considered safe therefore topical capsaicin must selectively desensitize C-fibre neurons while preserving function of possibly impaired larger fibre types. This required activity appears to be achieved with Axsain (0.075% capsaicin cream).

There are no known drug interactions when Axsain cream is used as concomitant therapy. When necessary, medications used to manage the pain of diabetic neuropathy or associated conditions such as depression, or drug therapy for completely unrelated conditions, can be used concurrently with Axsain with minimal concern for drug interactions.

Based on clinical studies, a burning sensation following application of Axsain is the most common adverse effect. Over 50% of the patients who use Axsain for painful diabetic neuropathy may experience burning pain with Axsain application. Since patients with painful diabetic neuropathy often present with hyperaesthesia or burning pain, they are particularly prone to the burning pain associated with Axsain application. Between ten and twenty percent of the patients experiencing this adverse effect may discontinue therapy because of the severity. For the majority of patients, however, the burning sensation appears to be well tolerated and the effect is temporary often diminishing or disappearing with continued regular use.

5.4. Dose and administration

Conventional dose ranging and percutaneous absorption studies have not been performed. Empirically, the 0.075% capsaicin formulation applied three to four times daily appears to be temporally appropriate and is preferred over the lower concentration of 0.025% for neuropathic pain.

5.5. **Risk/benefit**

The current treatment modalities available to provide relief from pain associated with diabetic neuropathy do not always provide adequate pain relief and their use either alone or as combination therapy can often be limited by adverse effects and drug interactions. Elderly diabetic subjects may be particularly vulnerable to these untoward effects. Axsain, containing 0.075% capsaicin, has no serious long term effects (53) and thus combines an excellent safety profile with effective treatment of the debilitating pain associated with diabetic neuropathy. The pain relief achieved has been demonstrated to be at least comparable with alternative therapies such as amytriptyline, whilst providing a favourable risk/benefit profile. These characteristics afford Axsain the attributes to be used either as monotherapy or as adjunctive therapy.

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