Intrathecal drug delivery systems (IDDSs) provide targeted drug delivery for chronic, intractable pain. Please see the brief summary on page 16. The intent of this summary is to present data from published scientific literature relating to the clinical and economic evidence of intrathecal drug delivery (IDD) for chronic intractable pain.

Overview

Opioid receptors were discovered in the central nervous system in the 1970s. Soon thereafter, many studies showed that when morphine is infused into the cerebrospinal fluid close to the spinal opioid receptors, it produces analgesia at a much lower dosage* and with fewer or milder adverse effects than when it is administered systemically. Consequently, intrathecal (IT) opioid infusion, or intrathecal drug delivery (IDD),** became an option for alleviating chronic pain, initially of cancer origin and later of nonmalignant origin, in patients who failed to respond to conventional pain therapies or did not tolerate systemic opioids due to their adverse effects.

IDD for chronic pain is achieved with an implantable system that consists of an infusion pump and an intraspinal catheter. The pump, which has a drug-containing reservoir, is placed in a subcutaneous pocket in the anterior abdominal wall. The catheter is inserted into the IT space of the spine, tunneled under the skin, and connected to the pump. The reservoir is refilled by a needle inserted through the skin. The IDD system in greatest use has a battery-operated pump, which is programmable with a handheld telemetry device that can set the pump to deliver a constant infusion, a greater infusion during certain periods of the day, or a single dose of drug at a specific time or times of the day. Also, the pump can store and transmit telemetry data on the patient, the drug being infused, the pump’s programming, reservoir volume, and performance data, and provide an audible signal when its battery power, reservoir volume, or temperature are below set thresholds. Constant-flow programming may be indicated when the infusion rate will be constant day and night.

Implantation of an IDD system should follow a successful trial of intraspinal opioid administration by epidural or IT injection, or by epidural or intrathecal infusion using an external pump.

Intrathecally administered opioids, such as morphine, can relieve neuropathic pain from irritation of a nerve root or peripheral nerve, nociceptive pain from irritation of pain-sensitive nerve fibers, and deafferentation pain from destruction of an ascending sensory system. Morphine and alternatively ziconotide, a calcium channel blocker with analgesic properties, are the only drugs approved by the Food and Drug Administration (FDA) for intrathecal infusion for pain.

* For a given analgesic effect, 1 mg of IT morphine is equivalent to about 300 mg of oral morphine or about 100 mg of intravenous morphine.

**A broader term that encompasses opioids and various adjuvant medications.

Serious complications of IDD system implantation, such as meningitis and wound infection may occur. Intrathecal morphine can produce generally tolerable and self-limiting adverse effects, most commonly pruritus, nausea and vomiting, urinary retention, and constipation. A noninfectious, granulomatous mass, which has been associated with morphine infusion, can develop at the tip of the infusion catheter to limit IDD and, if undiagnosed, produce neurologic injury including paralysis.
Overview (continued)

IDD is widely used in the United States for controlling chronic pain, most frequently failed back surgery syndrome (FBSS). This document presents results of studies of IDD, published in the peer-reviewed scientific literature, to determine the effectiveness and cost of IDD.

Effectiveness Data from IDD Studies for Chronic Pain

Introduction to Studies Published Before 2006

A number of studies of the effectiveness of IDD in treating chronic pain were published following FDA clearance of IDD and before 2006. Although patient-selection criteria varied considerably, these studies required that patients have pain refractory to medical or surgical therapies, or have intolerable adverse effects from systemic opioids. Exclusion criteria included major psychiatric disorders, drug habituation problems and unresolved issues of secondary gain, which can have a negative impact on pain management. Most of these studies assessed IDD effectiveness by measuring pain intensity before and after IDD system implantation with a numerical pain rating (NPR) scale or visual analog scale (VAS). Use of an NPR scale involves the patient giving a numerical assessment of pain severity usually between 0 for “no pain” and 10 for “worst possible pain,” and use of a VAS involves the patient placing a mark usually on a 10-cm line between 0 cm for “no pain” and 10 cm for “worst possible pain.” Many studies also determined the patients’ pre- and postimplantation physical functioning and disability levels, intake of oral/systemic analgesics, and satisfaction with IDD.

Introduction to Studies Published Since 2006

In the past decade, studies have examined mid-term results and focused on refining IDD effectiveness and safety. Table 1 summarizes studies of IDD effectiveness using morphine or ziconotide to treat chronic, intractable pain.

Table 1. Effectiveness Data from IDD Studies for Chronic Pain (listed chronologically starting with the most recent)

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Description</th>
<th>Results</th>
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<tbody>
<tr>
<td>Hamza, et al. 2015</td>
<td>This prospective, randomized, single-blind study compared long-term outcomes between patients trialed with IT boluses (cohort A) or continuous infusion (cohort B) before receiving an IDD system for treatment of severe, intractable, chronic, nonmalignant pain. 40 patients with similar demographics were randomly assigned to a trial using intermittent boluses or a trial using continuous infusion. All patients were gradually weaned to 50% of their baseline systemic opioids over 3 to 5 weeks before the trial. Those who had a successful trial weaned from all systemic opioids over the next 3 to 5 weeks. They were then opioid-free for 7 to 10 days before implantation of the Synchromed II programmable system. The inpatient trial protocol was single-blinded, placebo-controlled, and dose-escalating. In the bolus cohort, doses of 125 mcg, 240 mcg, and saline were administered at 24-hour intervals. In the continuous-infusion cohort, administration consisted of 5 mcg/hour, 10 mcg/hour, or saline.</td>
<td>One patient in each cohort had an unsuccessful trial, and 1 patient in each cohort received off-label medication. Two patients in the bolus-trial cohort and 1 in the continuous-infusion trial cohort were lost to follow-up. Both cohorts had similar baseline characteristics. Females comprised 58% (n=10) of cohort A and 61% (n=11) of cohort B. Mean age in both cohorts was 59.2 years, and duration of symptoms was 6.2 years in cohort A and 7.2 years in cohort B. There were no significant differences between the cohorts in worst or average pain, walking, normal work, general activity or mood BPI scores at any of the follow-up intervals. The significant improvements were measured at 6 months and sustained through 36 months. During the 36-month follow-up, the walking BPI scores of both cohorts improved significantly compared with baseline (P&lt;0.001). Improvement from baseline occurred at each follow-up time, ranging from 3.76 to 4.71 in cohort A and from 3.94 to 4.83 in cohort B.</td>
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Morphine was used except in cases of documented allergy, when an off-label medication was used instead. Achieving >50% pain relief, physical and behavioral function, and no or minimal response to saline defined a successful trial. IT dosing began at the dose for which 50% pain reduction was reported during trial. Follow-up occurred at 6, 12, 18, 24, and 36 months postimplant. Outcomes were assessed with the Brief Pain Inventory (BPI), which measures worst and average pain, physical function (walking, normal work, and general activity), behavioral function (mood, sleep, and relationships), IT dose, and systemic opioid use. The global Patient Reported Pain and Functional Improvement scale (0% to 100%) was also used. IT and oral opioid use was documented in morphine equivalents (MEs).

Both cohorts had significant improvements in normal work BPI scores (P<0.001) from baseline to 36 months. Improvement from baseline occurred at each follow-up time, ranging from 2.93 to 3.71 in cohort A and from 3.67 to 4.11 in cohort B. Both cohorts had significant improvements in general activity BPI scores (P<0.001) from baseline to 36 months. Improvement from baseline occurred at each follow-up time, ranging from 3.36 to 4.41 in cohort A and from 3.44 to 4.17 in cohort B. Both cohorts had significant improvements in mood BPI scores (P<0.001) from baseline to 36 months. Both cohorts had significant improvements in sleep BPI scores (P<0.001) from baseline to 36 months. Both cohorts had significant improvements in relation BPI scores (P<0.001) from baseline to 36 months.

Between 6 and 36 months sleep scores significantly worsened (P<0.017) in cohort B, although they remained low (4.06) and significantly lower than at baseline (P<0.001). In cohort A the mean sleep score was 3.82. Both cohorts had significant changes in relations BPI scores (P<0.001) from baseline to 36 months. The significant improvement was measured at 6 months, followed by significant increases between 6 and 36 months. However, these score increases remained lower than at baseline in both cohorts. Both cohorts had significant changes in enjoyment of life BPI scores (P<0.001) from baseline to 36 months. The significant improvement was measured at 6 months, followed by significant increases between 6 and 36 months. However, these score increases remained lower than at baseline in both cohorts. Mean enjoyment of life score was 4.47 in cohort A and 4.56 in cohort B.

According to the patient global impressions, the majority of patients in both cohorts reported >50% improvement in pain and from 26% to 75% improvement in function during the 36 months. Mean oral morphine use at baseline was 278.6 mg in cohort A and 230.44 mg in cohort B. Both groups decreased oral opioid usage significantly by 6 months postimplant (P<0.001). No statistically significant changes in oral opioid dosages occurred in cohort A, but cohort B had a moderate decrease in dosage between 24 (4.22 MEs) and 36 months (3.11 MEs).

During the study, there were no statistically significant changes in IT dose for cohort A. In cohort B, moderately significant changes occurred between months 6 and 36. Mean IT dose at 36 months was 0.47 MEs for cohort A and 0.51 MEs for cohort B.
In total, there were 4 infections that were treated with oral antibiotics and resolved, 1 case of pain at the pump site, 2 cases of peripheral edema that responded to treatment, and 2 cases of urinary retention, 1 of which resolved and the other of which was treated with a temporary indwelling bladder catheter on 2 occasions.

No significant difference in outcomes was associated with the trialing method. IT medication remained low and stable for 3 years, suggesting that chronic pain can be effectively managed for the long term without frequent medication adjustments. Furthermore, postimplant oral opioid use was extremely low.

In this study, IDD therapy provided significant and sustained pain relief, and improvement in physical and behavioral factors for patients with chronic nonmalignant pain.

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<td>Caraway, et al. 2015&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Ninety percent of patients were taking systemic opioids before implantation, and systemic opioid use decreased significantly after implantation (P&lt;0.001). All patients previously taking long-acting opioids (n=33) discontinued these within 1 month of implant. Total systemic opioid elimination was accomplished by 68% of patients at 1 month postimplant, 84% at 1 year, and 92% at 5 years. For patients taking short-acting opioids, the mean daily preimplantation dose of hydrocodone was 27.3 mg and of oxycodone was 33.2 mg. At 1 month postimplant, these doses were 27.8 mg and 26.3 mg, respectively. At 1 month, 60% of patients reported decreased pain (mean score change: -4.07) and at 1 year, 64% did (mean score change: -3.42). Compared with baseline scores, mean pain scores decreased significantly at 1 month (P&lt;0.001), 6 months (P&lt;0.001), 1 year (P&lt;0.001), and 5 years (P&lt;0.047). Ten patients (10%) underwent IDDS replacement or revision, 6 for end of battery life, and 4 for other reasons. Ten patients had catheter revisions. Only 1 patient was explanted because of therapy failure. IDD provided significant and lasting pain relief and an alternate route of delivery compared to systemic opioids with their associated side effects. Systemic opioid elimination can be accomplished in the majority of cases through appropriate patient selection, monitoring, and participation.</td>
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This prospective cohort study enrolled 58 patients with chronic nonmalignant pain who were trialed and maintained on low-dose IT therapy for 36 months. All patients had been referred to an academic pain practice following failure of other therapies, including nonsteroidal medications, antiepileptic and antidepressant medications for neuropathic pain, oral or transdermal opioids, interventional pain procedures, and SCS. Patients considered for trialing had documented evidence of nociceptive, neuropathic, or mixed pain from diagnoses including failed back surgery syndrome (FBSS), postlaminectomy pain syndrome, degenerative disc disease, lumbar spinal stenosis, nonoperative neurogenic claudication, complex regional pain syndrome type II, and scoliosis.

The trial procedure and medication management were described to all patients, who also saw a behavioral psychologist for pretrial evaluation. Before trial, there was a gradual 3-to-4-week opioid taper period followed by a 4-to-6-week opioid-free interval. Patients who experienced adequate analgesia with improved function (measured by physical and occupational therapists) without side effects were implanted with a Synchromed II 20-mL IDD system. Patients remained opioid-free in the interval between a successful trial and permanent implantation (usually 2 weeks).

Results were compared for the Multidimensional Pain Inventory (MPI), Global Pain Scale (GPS), and VAS before trial, and at 6, 12, 24, and 36 months after implant.

A total of 73 patients underwent trial, 60 were implanted, and 58 agreed to study enrollment; 57 patients completed the 36-month evaluation. Before trial, patients averaged 64 mg/day of oral/systemic MEs. Six patients had trialed oral opioid therapy, but presented opioid-free before trial. All patients were free of systemic opioids during the 36-month follow-up period with 1 exception. That patient required supplementation (20 mg/day hydrocodone from month 24 to 36) for a thoracic compression fracture. Another patient discontinued IDD therapy and returned to oral opioids.

Compared with pretrial values, VAS scores improved significantly at implant (P<0.001), 6 months (P<0.001), 12 months (P<0.001), 24 months (P<0.001), and 36 months, and GPS scores also improved significantly at each time period (P<0.005). The pretrial VAS of 7.8 ± 1.6 had decreased significantly to 4.6 ± 2.5 at 36 months. Similarly, the GPS of 63.5 ± 15.2 at trial was significantly reduced to 49.1 ± 17.3 at 36 months. MPI preimplant pain severity scores decreased significantly at 36 months (P<0.01) from 54.9 ± 6.1 to 47.4 ± 9.0. Pretrial and 36-month pain interference scores did not change significantly. MPI scores for pain severity and interference were significantly lower for nociceptive than for mixed pain, and IT doses were also lower at every time point for nociceptive than for mixed pain. The differences in the trial and 36-month doses for nociceptive vs. mixed pain were significant (P<0.01).

Postimplant GPS pain scores decreased steadily and significantly (P<0.001) during the 36 months. The GPS outcome “perceived need to receive more medication” showed significant and sustained efficacy of IDD without the need for more medication.

During the 36-month period, 8 patients reported worsened neuropathic pain, but no new pathology (such as granuloma) was identified by MRI evaluation. Four catheter malfunctions and 1 case of seroma formation required revision.

IT morphine doses for most patients stabilized in the 300 to 400 mcg range, which are among the lowest effective doses reported in the literature. Both perceived pain severity and dysfunction lessened during the study, an improvement not usually seen with oral opioid therapy.

No diagnostic group had a better response to low-dose IDD than any other.

Table 1. Effectiveness Data from IDD Studies for Chronic Pain (continued)
This randomized, double-blind, controlled, parallel-group study investigated the efficacy of IT morphine by reducing the opioid dose in 1 group every week for 10 weeks. Twenty-four patients being treated with IDD for >12 months were randomly assigned to receive no change in dose or a 20% dose reduction every week. VAS pain score and study withdrawal for lack of efficacy were the primary outcomes.

The Oswestry Disability Index (ODI), Hospital Anxiety and Depression (HAD) scale, and Coping Strategies Questionnaire (CSQ) were used to assess function and psychological factors.

Nine of the 24 eligible patients decided not to participate; 15 were randomized to the control group (n=5) or the dose-reduction group (n=10). In the control group, 2 patients had mechanical back pain and 3 had FBSS. In the dose-reduction group, 3 patients had mechanical back pain, 6 had FBSS, and 1 had postsurgery abdominal pain. The median age of patients was 58 years, and the median duration of symptoms before study participation was 26 months. There were no significant differences between the groups at baseline, except that the control group had a significantly higher morphine dose at baseline (60 mg/day for the control group vs. 50 mg/day for the dose-reduction group).

Seven patients withdrew from the study prematurely, all from the dose-reduction group, resulting in a 70% dropout rate. All the dropouts reported worsening pain.

The VAS in the dose-reduction group was significantly lower at baseline than at last observation (P=0.002). VAS did not change significantly for the control group (P=0.188). ODI scores in the dose-reduction group were also significantly lower at baseline than at last observation (P=0.027), but no such difference was noted for the control group (P=0.063). In the dose-reduction group, moderately important clinical changes occurred for 40% of the patients, and a substantially important increase in pain was reported by 30% of patients. In the control group, nonsignificant changes occurred in 40% of patients, minimally clinically important changes in 40%, and clinically substantial increase in pain in 20%.

Statistically and clinically significant increases in pain in the dose-reduction group, plus its high dropout rate, suggest the efficacy of IDD morphine in managing chronic noncancer pain.

NPR measurements improved significantly between baseline and 4 years for pain intensity, pain relief, coping, self-efficacy, depression, quality of life, housework, mobility, sleep, and social life (P<0.001). All of these improvements were sustained between 4 and 13 years, except for a small increase in pain intensity at 13 years (5.3) vs. 4 years (4.95). Complication rates were equivalent to 0.111 events per patient year, and side effects resolved with time or medication. Long-term benefits of IDD therapy were not accompanied by an escalation in opioid dose. Ninety percent of patients reported satisfaction with the therapy and considering IDD to be “worthwhile.”

| Raphael, et al. 2013²⁰ | This randomized, double-blind, controlled, parallel-group study investigated the efficacy of IT morphine by reducing the opioid dose in 1 group every week for 10 weeks. Twenty-four patients being treated with IDD for >12 months were randomly assigned to receive no change in dose or a 20% dose reduction every week. VAS pain score and study withdrawal for lack of efficacy were the primary outcomes. The Oswestry Disability Index (ODI), Hospital Anxiety and Depression (HAD) scale, and Coping Strategies Questionnaire (CSQ) were used to assess function and psychological factors. | Nine of the 24 eligible patients decided not to participate; 15 were randomized to the control group (n=5) or the dose-reduction group (n=10). In the control group, 2 patients had mechanical back pain and 3 had FBSS. In the dose-reduction group, 3 patients had mechanical back pain, 6 had FBSS, and 1 had postsurgery abdominal pain. The median age of patients was 58 years, and the median duration of symptoms before study participation was 26 months. There were no significant differences between the groups at baseline, except that the control group had a significantly higher morphine dose at baseline (60 mg/day for the control group vs. 50 mg/day for the dose-reduction group). Seven patients withdrew from the study prematurely, all from the dose-reduction group, resulting in a 70% dropout rate. All the dropouts reported worsening pain. The VAS in the dose-reduction group was significantly lower at baseline than at last observation (P=0.002). VAS did not change significantly for the control group (P=0.188). ODI scores in the dose-reduction group were also significantly lower at baseline than at last observation (P=0.027), but no such difference was noted for the control group (P=0.063). In the dose-reduction group, moderately important clinical changes occurred for 40% of the patients, and a substantially important increase in pain was reported by 30% of patients. In the control group, nonsignificant changes occurred in 40% of patients, minimally clinically important changes in 40%, and clinically substantial increase in pain in 20%. Statistically and clinically significant increases in pain in the dose-reduction group, plus its high dropout rate, suggest the efficacy of IDD morphine in managing chronic noncancer pain. |
| Duarte, et al. 2012²¹ (abstr) | This prospective, longitudinal, single-center study investigated the long-term use of IDD by following 36 patients for 13 years. They were receiving IT therapy to treat either lower back pain (33%) or FBSS pain (67%).¹¹ | NPR measurements improved significantly between baseline and 4 years for pain intensity, pain relief, coping, self-efficacy, depression, quality of life, housework, mobility, sleep, and social life (P<0.001). All of these improvements were sustained between 4 and 13 years, except for a small increase in pain intensity at 13 years (5.3) vs. 4 years (4.95). Complication rates were equivalent to 0.111 events per patient year, and side effects resolved with time or medication. Long-term benefits of IDD therapy were not accompanied by an escalation in opioid dose. Ninety percent of patients reported satisfaction with the therapy and considering IDD to be “worthwhile.” |
This prospective, long-term cohort study followed 61 consecutive patients treated with low-dose IDD for severe intractable noncancer pain for 3 years. All patients had previously failed multiple medical management approaches. Patients were weaned to 50% of baseline systemic opioids over 3 to 5 weeks before trial. After a successful trial, the remaining opioids were discontinued over 3 to 5 weeks, followed by a 7-to-10 day opioid-free period before implant. Inpatient trials used a single-blind, placebo-controlled, dose-escalating protocol. Pain relief and physical function were evaluated for 24 hours after each IT dose (0.25 mg morphine, 0.5 mg morphine, or 0.5 mL of saline [placebo]). Assessments included the BPI and the global Patient Reported Pain and Functional Improvement scales. Postimplant follow-up occurred at 6, 12, 18, 24, and 36 months.

Most (58/61) patients proceeded to implant. Sixty percent of the patients were female, mean age was 59.2 years, and pain had endured for an average of 6.2 years. Worst and average pain decreased significantly from baseline to 36 months (P=0.012 and P<0.001, respectively). Between baseline and 36 months, mean worst pain scores decreased by 54.2% and average pain scores by 47.4%. Composite physical function scores (general activity, walking, and normal work) improved significantly from baseline to 36 months (P<0.001). Patients reported pain reduction of 65.2% and functional improvement of 42.7%. More than 75% improvement was reported by almost 38% of patients, and more than 50% improvement by 72.4%. BPI enjoyment scores (mood, relations, sleep) improved significantly from baseline to 36 months (P<0.001).

Oral opioid consumption decreased significantly from 6 to 36 months (P<0.001). Over 3 years of treatment, the average increase in dose was 11.4%, with the largest increase from 18 to 24 months, and stabilization between 24 and 36 months. Mean oral opioid dose was 126.71 mg/day at baseline and had decreased to 3.80 mg/day at 3 months.

Mean IT opioid doses were 1.4 MEs/day at 6 months and 1.48 MEs/day at 36 months. Type of pain, duration of symptoms, or initial IT doses did not correlate with outcomes. In this study, patients responded to morphine monotherapy, without requiring increased doses, medication changes or admixtures.

There were 3 cases of wound infection, 2 of peripheral edema, 3 of pruritus, and 2 of seroma. “Low-dose opioids can provide sustained significant improvement in pain and function for long-term follow-up in chronic noncancer pain.”

In this retrospective review, 22 patients underwent systemic opioid taper and a 5-week opioid-free period before an increasing dose, inpatient IDD trial starting at 25 mcg and increasing to 50, 100, 200, or 400 mcg until pain relief was achieved. Following a successful IDDS trial during week 6, patients remained opioid-free for 10 to 14 days before permanent implantation and they never resumed systemic opioid therapy thereafter.

VAS scores were obtained at initial visit, at week 6 after the opioid-free period and before trial, after each dose escalation, at 1 month postimplant, and at last visit.

Most (20/22) patients were implanted. Two patients were switched to an off-label medication after failing to receive adequate efficacy with IT morphine. Follow-up ranged from 12 to 44 months.

A year postimplant, the VAS for pain was significantly lower (7.3 ± 1.9 before opioid taper, 7.15 after opioid-free period, and 3.9 ± 2.6 a year postimplant), and function, evaluated by physical and occupational therapists, had improved. At the dose deemed to be efficacious, significant improvement occurred at rest, moving from supine to sitting and sitting to standing, and in gait, lower body dressing, picking up objects from the floor, and overhead reaching.
The lowest initial dose that provided efficacy was 50 mcg/day, with the average dose being 140 mcg/day. At 12 months the average dose was 335 mcg/day. No patients were taking supplemental oral opioids.

Analgesia was maintained with microgram doses, with a dose-response relationship for effective analgesia of <400 mcg IT morphine; most patients achieved analgesia with doses in the 100 to 200 mcg range.

Lower effective IT doses would be expected to enhance patient safety.

The 57 patients initially treated with IDD had diagnoses of FBSS (n=28), neuropathic pain including CRPS (n=16), visceral pain (n=5), malignancy (n=2), and miscellaneous (n=6). There were 27 males and 30 females and the mean age was 49.7 years. Records for 43 patients were available for 3-year follow-up.

VAS decreased from 7.7 at baseline to 5.7 at 3 years, a statistically significant reduction from baseline to all subsequent measurement times (P<0.001). There was a decreasing trend in the percentage of patients who reported >50% pain relief, from 47% at first refill to 18% at 3 years.

Systemic opioid consumption fell significantly from 183.9 mg/day MEs at baseline to 57.6 mg/day at 3 years (P<0.001). This represented a 69% reduction from baseline. A significant correlation was noted between baseline oral opioid dose and VAS scores at 3 years (r=0.49, P=0.001). Preimplant opioid consumption inversely correlated with treatment success.

IT doses gradually increased from 6.5 mg/day initially to 12.2 mg/day at 3 years. There were statistically significant increases in IT doses between IDD implementation and each subsequent follow-up time.

Ten of the 57 patients experienced 14 complications: 5 had infections, 3 had catheter revisions, 2 had seroma at the pump site, and 2 developed IT granuloma. By the end of the study period, 10 pumps had been removed and 2 patients were not using their pumps. The resulting treatment failure rate was 24%.

IDD produced long-term pain reduction, and decreased systemic opioid consumption by almost half.
Thirty patients with chronic pain unresponsive to comprehensive medical management (CMM) were weaned off opioids before trialing IDD. Patients filled out the McGill Pain Questionnaire (MPQ) and VAS before and after implant at 3, 12, and 24 months. The MPQ evaluative component improved significantly by 66% over 24 months, the effective component by 59%, and the sensory component by 32%. VAS improved by 55%. Average morphine infusion rate increased from $0.23 \pm 0.14$ initially to $0.80 \pm 0.45 \text{ mg/day}$ at the 24-month follow-up ($P<0.05$). Twelve of 13 patients returned to work full-time, and 14 of 17 retirees required less assistance, with 8 no longer requiring live-in assistance. The reduced level of chronic pain led to improved social, work, and family relationships and quality of life. Among working-age patients, 92% returned to full-time work, and 82% of retirees required less assistance.

This study was a retrospective chart review of 101 patients with low back pain from 8 centers, who were treated with IDD for at least 2 years and had at least 12 refills. Charts were available for 58 women and 43 men. Mean age was 55.7 years (32 to 84 years). Data were extracted from a total of 2,407 visits, 101 initial visits, 1,725 refill visits, and 581 other visits. Baseline pain data came from 89 pain patients who had a mean pain score of 7.7 on a 1 to 10 VAS scale. Refill visits occurred on average every 1.5 months. Morphine was the most frequently used medication (47.7% of total medications given), and 89% had daily a morphine dose no greater than 25 mg/day. The mean infusion flow rate for morphine was $0.37 \pm 0.22 \text{ mL/day}$.

At last visit, 94% of patients were receiving constant-flow treatment, which had been maintained from between 1 to 3 months and >30 months postimplant. Programming changes occurred at 992 visits, usually for modification of constant-flow rates. Continued experience reduced the need for programming changes. Many patients with nonmalignant low-back pain could use a constant-flow pump, either as a replacement or to initiate IDD therapy. This would reduce cost and the need for replacement surgery.

Twenty-four patients with vertebral fractures due to osteoporosis received IDD after a successful trial of IT medication. Evaluation was by VAS and the Questionnaire of the European Foundation of Osteoporosis (QUALEFFO) 1 year postimplant. VAS declined from 8.7 pretrial to 1.9 at 1 year postimplant. Mean IT morphine dose at 1 year was 16.32 mg/day. QUALEFFO dropped from 114.7 to 79.1, with significant improvements in quality of daily life, domestic work, ambulation, and perception of health status. Patients reported improved function and satisfaction with therapy, and required no systemic opioid medications. Complications included 1 wound infection and 1 delayed wound healing.

"Continuous intrathecal administration of morphine appears to be an alternative therapy to conventional analgesic drug delivery and has advantages in those patients who have severe side effects with systemic administration of analgesics."

### Table 1. Effectiveness Data from IDD Studies for Chronic Pain (continued)

<table>
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<tr>
<th>Study</th>
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<tbody>
<tr>
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<tr>
<td>Shaladi, et al. 2007&lt;sup&gt;27&lt;/sup&gt; (abstr)</td>
<td>Twenty-four patients with vertebral fractures due to osteoporosis received IDD after a successful trial of IT medication. Evaluation was by VAS and the Questionnaire of the European Foundation of Osteoporosis (QUALEFFO) 1 year postimplant. VAS declined from 8.7 pretrial to 1.9 at 1 year postimplant. Mean IT morphine dose at 1 year was 16.32 mg/day. QUALEFFO dropped from 114.7 to 79.1, with significant improvements in quality of daily life, domestic work, ambulation, and perception of health status. Patients reported improved function and satisfaction with therapy, and required no systemic opioid medications. Complications included 1 wound infection and 1 delayed wound healing. &quot;Continuous intrathecal administration of morphine appears to be an alternative therapy to conventional analgesic drug delivery and has advantages in those patients who have severe side effects with systemic administration of analgesics.&quot;</td>
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</tbody>
</table>
This prospective, open label, multi-center study assessed the safety and efficacy of long-term IT ziconotide infusion in 155 enrolled patients with severe chronic pain who had been responsive to short-term IT ziconotide. This was a double-blind, placebo-controlled study following up on patients from studies by Staats et al. 2004 and Wallace et al. 2006. One hundred and forty-five patients were included in the modified intention-to-treat population (101 with nonmalignant pain). Ten patients did not have Visual Analog Scale of Pain Intensity (VASPI) data available.

The mean change in monthly VASPI scores through 12 months showed significant improvements at (P<0.0001) and the % change from baseline to 12 months also showed significant improvement at all time-points (P<0.0001).

All 155 enrolled patients were included in the safety analysis. The attrition rate due to death, adverse event (AE) and lack of efficacy was substantial, with only 31/155 remaining in the study at 1 year. To avoid bias due to patient discontinuation during these 12 months, post hoc analyses were performed on the cohort of 31 patients remaining after 12 months and demonstrated that there was no attenuation of analgesic effect (P<0.0001). Most patients (94.8%) reported at least 1 AE considered related to ziconotide.

### Intrathecal Ziconotide

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Study Details</th>
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<tbody>
<tr>
<td>Ellis, et al. 2008</td>
<td>This prospective, open label, multi-center study assessed the safety and efficacy of long-term IT ziconotide infusion in 155 enrolled patients with severe chronic pain who had been responsive to short-term IT ziconotide. This was a double-blind, placebo-controlled study following up on patients from studies by Staats et al. 2004 and Wallace et al. 2006. One hundred and forty-five patients were included in the modified intention-to-treat population (101 with nonmalignant pain). Ten patients did not have Visual Analog Scale of Pain Intensity (VASPI) data available.</td>
</tr>
<tr>
<td>Wallace, et al. 2008</td>
<td>This was a prospective multicenter open-label study of 644 patients with severe chronic pain. Ziconotide titration was followed by long-term infusion, and efficacy of pain reduction measured by VASPI. During the course of treatment, 576 patients withdrew, primarily within the first 3 months due to lack of efficacy or AEs. Patients received ziconotide therapy for a median of 67.5 days (range, 1.2-1,215.5 days), with 119 patients (18.5%) receiving therapy for 360 days. The median duration of ziconotide therapy was 67.5 days (range, 1.2-1,215.5 days), and the mean dose at last infusion was 8.4 mcg/d (range, 0.048-240.0 mcg/d). Median VASPI scores at baseline, 1 month, and the last available observation up to 2 months were 76 mm (range, 4-100 mm), 68 mm (range, 0-100 mm), and 73 mm (range, 0-100 mm), respectively. Most patients (99.7%) experienced more than 1 AE, although most were of mild (43.5%) or moderate (42.3%) severity, and 58.6% were considered unrelated to ziconotide. The most commonly reported AEs (≥25% of patients) included nausea, dizziness, headache, confusion, pain, somnolence, and memory impairment. Clinically significant abnormalities (&gt;3 times the upper limit of normal) in creatine kinase levels were reported in 0.9% of patients at baseline, 5.7% at month 1, and 3.4% at ziconotide discontinuation. No drug-related deaths, IT granulomas, or permanent adverse sequelae occurred with ziconotide therapy. Among patients with VASPI scores ≥50 mm at baseline who completed 1 month of therapy, 32.7% had a ≥30% improvement in VASPI score at 1 month, while 15.3% who had baseline VASPI scores &lt;50 mm and completed 1 month of therapy had a ≥30% improvement in VASPI score at 1 month.</td>
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</table>
Wallace, et al. 2006

This study evaluated the efficacy and safety of ziconotide in 258 patients in a randomized double-blind, placebo-controlled trial. The patients suffered from severe chronic nonmalignant pain of varying etiologies unresponsive to conventional therapy with a VAS of pain intensity greater than 50 mm. The starting and maximum dose of ziconotide was 0.4 mcg/hour and 7.0 mcg/hour.

Average VASPI decreased from baseline by 31.2% in ziconotide-treated patients and 6% in the placebo-treated group. The number of AEs was significantly higher in the ziconotide-treated group compared to placebo during the initial titration phase of the trial. The AEs include amblyopia, dizziness, nystagmus, pain, urinary retention, abnormal gait, nausea, and vomiting. The authors concluded that the high number of AEs was due to the rapid titration and high dose of ziconotide. However, the drug provided significant analgesia.

Rauck, et al. 2006

This study evaluated the efficacy of ziconotide in 220 patients with predominately noncancer neuropathic pain (58% FBSS) and a preexisting SynchroMed drug infusion system. A drug withdrawal and stabilization protocol was used to convert patients from IT therapy to ziconotide or placebo. Ziconotide was initiated at 0.1 mcg/hour (2.4 mcg/day) and increased from 0.05-0.1 mcg/hour to a final dose of 0.29 mcg/hour (6.96 mcg/day).

Clinical Global Impression (CGI) and Global McGill Pain Relief scores were used. Ziconotide significantly reduced VASPI from baseline to week 3 by 15.7% vs. placebo 7% (P=0.036). CGI satisfaction improved by 28% with ziconotide (“a lot” or “complete” satisfaction) compared with 12% with placebo. The Global McGill Pain Relief total score was significantly reduced with ziconotide compared to placebo, although there was a 24% mean decrease in weekly opioid use (MEs) from pretreatment stabilization to week 3 with ziconotide, which did not differ from the 17% decrease with placebo (P=0.44).

Discontinuation rates due to AEs and serious AEs were comparable for both groups: 11.6% of ziconotide patients reported 19 serious AEs and 9.3% of placebo patients reported 25 serious AEs (P=0.57). Serious AEs were considered drug related in 1.8% of ziconotide and in 1.9% of placebo patients. The authors concluded that slow titration of ziconotide to a low maximum dose resulted in significant improvement in pain and was better tolerated than in previous controlled trials that used faster titration and a higher mean dose.

Staats, et al. 2004

This study assessed the safety and efficacy of IT ziconotide in patients with refractory to conventional treatment for pain in a double-blind, placebo-controlled, randomized trial involving 32 centers in the United States, Australia, and Netherlands. There were 111 patients either with cancer or AIDS and a mean VASPI score of 50 mm or greater randomly assigned (2:1) to ziconotide or placebo. Ziconotide was titrated over 5 to 6 days, followed by a 5-day maintenance phase for responders and crossover of nonresponders to the opposite group.

Mean VASPI scores improved by 53% in the ziconotide group and 18% in the placebo through titration (P<0.001) and similarly by 51% and 18%, respectively, at the end of the efficacy phase (P<0.001). Five patients achieved complete pain relief. CPRS pain relief was moderate to complete in 53% of the ziconotide group and moderate in 17.5% of the placebo (P<0.001). Serious AEs were experienced in 22/72 patients receiving ziconotide and 4/40 patients receiving placebo. Most of the AEs appeared related to the drug and not the pump. There were 5 cases of meningitis in the ziconotide group and 2 for placebo, all with external pumps.

### Table 1. Effectiveness Data from IDD Studies for Chronic Pain (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Conditions</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wallace, et al. 2006</td>
<td>258</td>
<td>Severe chronic nonmalignant pain</td>
<td>Ziconotide</td>
<td>Decreased VASPI by 31.2%</td>
</tr>
<tr>
<td>Rauck, et al. 2006</td>
<td>220</td>
<td>Predominately noncancer neuropathic pain</td>
<td>Ziconotide</td>
<td>Reduced VASPI by 15.7%</td>
</tr>
<tr>
<td>Staats, et al. 2004</td>
<td>111</td>
<td>Refractory cancer or AIDS</td>
<td>Ziconotide</td>
<td>Improved VASPI by 53%</td>
</tr>
</tbody>
</table>

**Table:** Effectiveness Data from IDD Studies for Chronic Pain (continued)
Summary of Studies Published Before 2006
Numerous studies, including 7 prospective cohort studies,\textsuperscript{10,33-38} and 5 retrospective cohort studies\textsuperscript{6,11,39-41} examined the efficacy and safety of IDD therapy. In 7 studies where results of trial IDD were reported,\textsuperscript{10,34-37,42} an IDD system was implanted in 88\% (250/285) of the trialed patients. Follow-up averaged 33 months (12 to 53 months). In all 12 studies, IDD was effective in controlling chronic pain at long-term follow-up.\textsuperscript{9,11,34,36,37,39,40} In a comparative study conducted by Doleys and colleagues,\textsuperscript{39} patients who received IDD had a significant decrease in pain intensity, whereas patients who participated in a 4-week residential pain and rehabilitation program or received standard medical therapy that emphasized use of oral opioids did not.

In 4 studies,\textsuperscript{36,39,41,38} 84\% (109/129) of patients reported good-to-excellent results from IDD, and in 5 other studies,\textsuperscript{9,11,34,37,40} 86\% (255/261) of patients reported satisfaction with IDD. In 9 studies\textsuperscript{9,11,34-37,41,40} IDD improved physical functioning, and in 2 studies\textsuperscript{33,39} it did not. IDD was also associated with decreased disability,\textsuperscript{33-35} improved work status,\textsuperscript{11,34,38} and reduced use of systemic opioids.\textsuperscript{34-36,38-41}

Ten studies specifically described complications in 535 patients.\textsuperscript{9-11,33-38,40} Catheter-related problems, including migration, kinking, disconnection, and occlusion, occurred in 16\% of these patients. Pump-related problems, including pump pocket infection, pump shift in position, and pump malfunction and failure, occurred in 8\% of patients.

Summary of Studies Published Since 2006
Seven of the 11 studies of IT morphine summarized in Table 1 were prospective\textsuperscript{17,19-22,25,27} and 4 were retrospective.\textsuperscript{18,23,24,26} Ten of the prospective studies documented significant decreases in pain between baseline and follow-up periods extending from 1 to 13 years. Only 1 study reported a decreasing trend in patients reporting >50\% pain relief, although pain at 3 years postimplant was still significantly less than at baseline.\textsuperscript{24} The 11th study was a randomized, controlled, double-blind study in which IT medication was decreased by 20\% each week in 1 group while a parallel control group had no change in IT medication.\textsuperscript{20} The 70\% of patients who dropped out of the dose-reduction group reported worsening pain. One study documented significantly lower pain severity and interference scores, as well as lower IT doses, for patients with nociceptive rather than with mixed pain.\textsuperscript{19}

Significant improvement in function was noted in all of the studies that assessed function.\textsuperscript{17,21-23,25,27} This included significant improvement in scores for walking, normal work and general activity (BPI, QUAL-EFFO). In 1 study, 12 of 13 patients returned to work, and 14 of 17 retirees required less assistance, with 8 no longer needing live-in assistance.\textsuperscript{25} Quality of life, reflected in evaluations of mood, sleep, relations, and enjoyment, had also improved significantly at 1 and 3 years postimplant in 4 studies.\textsuperscript{17,21,22,27} Two studies queried patients about their therapy; 90\% of patients in 1 study expressed satisfaction with their treatment,\textsuperscript{21} and perception of health status significantly improved in the other.\textsuperscript{27}

The past decade has seen increasing interest in low-dose IT therapy and discontinuation of systemic opioids after IDD implantation. The success of these strategies was first demonstrated by Hamza et al.\textsuperscript{22} and Grider et al.\textsuperscript{23} Although their pretrial/implantation opioid-weaning protocols differed, effective analgesia was achieved with an IT dose of <400 mcg morphine per day. Both of these centers have since published results at 36 months.\textsuperscript{17,19} In 1 study, IT doses stabilized in the 300 to 400 mcg range.\textsuperscript{19} In the other study, a moderately significant change in IT dose for 1 cohort occurred between 6 and 36 months, although the mean dose at 36 months was still low (0.47 MEs for 1 cohort and 0.51 MEs for the other). Staats et al. reported that 89\% of their patients had daily morphine doses no greater than 25 mg/day at 2 years.\textsuperscript{26} Duarte et al. also found that long-term efficacy was not accompanied by increases in IT opioid doses.\textsuperscript{21} However, 2 studies found that IT doses increased postimplant, from 0.23 mg/day to 0.80 mg/day at 24 months,\textsuperscript{25} and from 6.5 mg/day to 12.2 mg/day over 3 years.\textsuperscript{34} These studies were conducted before low-dose IT therapy was a subject for investigation.

Significant decreases\textsuperscript{17,18,22,24} or total elimination of oral opioids\textsuperscript{19,23,27} postimplant occurred in 7 studies. This achievement speaks to the efficacy of IDD and would be expected to improve patient safety and the cost-effectiveness of therapy. Indeed, the independent ECRI found that IDD therapy was associated with a decrease in the amount of other drugs taken or in the proportion of patients taking other drugs.\textsuperscript{43} And according to a Cochrane review, IDD patients were less likely than those taking oral opioids to discontinue treatment due to side effects or to have insufficient pain relief.\textsuperscript{44}

Among 334 patients in 7 studies,\textsuperscript{17-19,21,22,24,27} there were 14 cases of infection, 1 of delayed wound healing, 7 of peripheral edema, 5 of pruritus, 6 of seroma, 4 of urinary retention, 1 of pain at the pump site, 2 of granuloma, 7 of catheter malfunction or breakage, 13 catheter revisions, 10 IDD system revisions or replacements, 8 cases of worsening pain, 11 pumps explanted, and 4 patients not using their pumps or withdrawing from IDD therapy. Duarte et al. calculated a complication rate of 0.111 events per patient per year.\textsuperscript{21}
Three randomized, placebo-controlled trials of ziconotide have established its efficacy in treating chronic pain. Furthermore, all of the ziconotide studies summarized in Table 1 documented significant pain relief. Frequent AEs, more likely related to rate of dose increase rather than to absolute dose, suggest that ziconotide has a narrow therapeutic window. Accordingly, low initial dose and slow titration (increments of 0.5 to 1.0 mcg every several days) are recommended by the Polyanalgesic Consensus Conference (PACC), with a maximum dose per day of 19.2 mcg. No cases of ziconotide overdose or granuloma formation have been reported with ziconotide. Ziconotide is contraindicated in patients with a history of psychosis.

**Cost of IDD for Chronic Pain**

Table 2 summarizes recent studies of the cost-effectiveness of IDD therapy compared to CMM or when systemic opioids are eliminated postimplant.

**Table 2. Studies of the Cost of IDD for Chronic Pain (listed chronologically starting with the most recent)**

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Description</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hatheway, et al.</td>
<td>Claims data from commercial and Medicare databases in the United States were searched for patients who had an IDDS, used systemic opioids before implant, and had 12 months pre- and 13 months postimplant continuous medical and pharmacy coverage.</td>
<td>A total of 389 patients met inclusion criteria and 51% completely eliminated systemic opioids postimplant. 12% within the 30-day postimplant washout period and an additional 39% by the end of the 1-year horizon. Patients who eliminated systemic opioids were more likely to be 30 to 39 years old or &gt;80 years old and less likely to be 50 to 59 years old. They were also more likely to live in the Midwest and have a diagnosis of sleep apnea. Systemic opioid elimination within 120 to 210 days postimplant was associated with a reduction of $3,388 to $4,465 in inpatient and outpatient expenditures, and $4,689 to $5,571 in inpatient, outpatient, and drug expenditures. Complete elimination of systemic opioids resulted in a 10% to 17% reduction in yearly inpatient, outpatient and drug expenditures. These analyses of IDD patients with diverse pain etiologies, treated by many types of physicians with various opioid management protocols, and involving a variety of payment plans documented significantly lower expenditures for patients who eliminated systemic opioids postimplant compared to those who did not.</td>
</tr>
<tr>
<td>Guillemette, et al.</td>
<td>This retrospective database study analyzed claims data to evaluate the economic effects of IDD vs. CMM based on health services utilization and costs of care before and after IDD implantation.</td>
<td>A total of 555 noncancer pain patients received an IDD system within a 3-year period, and costs were standardized using national pricing over a 6-year cycle (3 years pre- and 3 years postimplant). Actuarial cost projections were generated over a 30-year horizon at different reimplantation rates. First-year postimplant costs were $17,317 more for IDD than CMM. Breakeven for IDD occurred soon after the second year postimplant. Subsequent lifetime savings were $3,111 annually for IDD vs. CMM. Patients with noncancer pain who are treated with IDD may experience reduced future medical costs compared to those treated with conventional therapies. The longer the reimplantation interval, the greater the savings, with the initial cost of the system and implantation recouped shortly after the second year of use.</td>
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</tbody>
</table>
Table 2. Studies of the Cost of IDD for Chronic Pain (continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Methodology</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kumar, et al. 2013⁴⁹</td>
<td>This study used a Markov model to derive quality-adjusted life years (QALYs) gained in a comparison of IDD with CMM and to calculate costs (drugs, physician visits, laboratory tests, scans, and hospitalizations) in 2011 CAN dollars.</td>
<td>The 10-year total costs were $61,442 for IDD and $48,408 for CMM. The incremental cost-effectiveness ratio (ICER) of 1.1508 per QALY resulted in an incremental cost of $13,034, and an ICER/QALY gain of $11,326. There was a 50% to 84% probability of IDD providing a cost-effective alternative to CMM at a willingness to pay (WTP) of $14,200/QALY and $20,000/QALY, respectively. IDD is cost effective compared with CMM in the management of chronic noncancer pain.</td>
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</table>

Table 2 Summary

Between 1991 and 2002, 3 studies⁵⁰-⁵² showed that the mean cost of IDD, which in the first year includes trial IDD and IDD system implantation, becomes substantially less in the second year after implant. One study that used actual cost indicated that IDD became cost-effective compared to CMM beyond 28 months of use.⁵² The study that used a cost model⁵⁰,⁵¹ found that this time period ranged from 12 to 22 months for selected patients.

In an era of cost containment, 3 recent studies provide additional insights. Guillemette et al. analyzed claims data to compare the costs of IDD to CMM.⁴⁸ As in the earlier studies, they found IDD was more costly than CMM, by $17,317, than CMM in the first year. However, breakeven for IDD occurred soon after the second year and subsequent lifetime savings favored IDD by $3,111 annually. Using a Markov model, Kumar et al. also compared the costs of IDD and CMM.⁴⁹ Total costs over 10 years were $61,442 for IDD and $48,408 for CMM. The ICER/QALY gained resulted in a 50% to 84% probability of IDD providing a cost-effective alternative to CMM at a WTP of $14,200/QALY and $20,000/QALY, respectively.

Hattheway et al. analyzed commercial claims data to assess the comparative costs for IDD patients who eliminated systemic opioids vs. those who did not.⁴⁷ Patients who eliminated systemic opioids postimplant realized total savings (inpatient, outpatient and drug costs) of $4,689 to $5,571, resulting in a yearly 10% to 17% reduction in expenditures.

Conclusions

Decades of IDD therapy continue to demonstrate its effectiveness in controlling chronic pain, and new, low-dose and systemic opioid-reduction strategies have proven to be both clinically effective and cost-efficient. Economic studies indicate that IDD treatment for chronic pain becomes more cost-effective than CMM after about 2 years of use.

References


SynchroMed® II Drug Infusion System Brief Statement:
Product technical manuals and the appropriate drug labeling must be reviewed prior to use for detailed disclosure.

Indications:
US: Chronic intraspinal (epidural and intrathecal) infusion of preservative-free morphine sulfate sterile solution in the treatment of chronic intractable pain, chronic intrathecal infusion of preservative-free ziconotide sterile solution for the management of severe chronic pain, and chronic intrathecal infusion of Lioresal® Intrathecal (baclofen injection) for the management of severe spasticity; chronic intravascular infusion of fluorouracil (FUDR) or methotrexate for the treatment of primary or metastatic cancer. Outside of US: Chronic infusion of drugs or fluids tested as compatible and listed in the product labeling.

Contraindications:
Infection; implant depth greater than 2.5 cm below skin; insufficient body size; spinal anomalies; drugs with preservatives, drug contraindications, drug formulations with pH ≤3, use of catheter access port (CAP) kit for refills or of refill kit for catheter access, blood sampling through CAP in vascular applications, use of Personal Therapy Manager to administer opioid to opioid-naive patients or to administer ziconotide.

Precautions:
Monitor patients after device or catheter replacement for signs of underdose/overdose. Infuse preservative-free (intraspinal) saline or, for vascular applications, infuse heparinized solutions therapy at minimum flow rate if therapy is discontinued for an extended period of time to avoid system damage. EMI may interfere with programmer telemetry during pump programming sessions. EMI from the SynchroMed programmer may interfere with other active implanted devices (e.g., pacemaker, defibrillator, neurostimulator).

Adverse Events:
Include, but are not limited to, spinal/vascular procedure risks; infection; bleeding; tissue damage, damage to the system or loss of; or change in, therapy that may result in additional surgical procedures, a return of underlying symptoms, and/or a clinically significant or fatal drug under- or overdose. Refer to appropriate drug labeling for indications, contraindications, warnings, precautions, dosage and administration, screening procedures and underdose and overdose symptoms and methods of management. Physicians must be familiar with the drug stability information in the product technical manuals and must understand the dose relationship to drug concentration and pump flow rate before prescribing pump infusion. Implantation and ongoing system management must be performed by individuals trained in the operation and handling of the infusion system. An inflammatory mass that can result in serious neurological impairment, including paralysis, may occur at the tip of the implanted catheter. Clinicians should monitor patients on intraspinal therapy carefully for any new neurological signs or symptoms, change in underlying symptoms, or need for rapid dose escalation.

Inform patients of the signs and symptoms of drug under- or overdose, appropriate drug warnings and precautions regarding drug interactions, potential side effects, and signs and symptoms that require medical attention, including prodromal signs and symptoms of inflammatory mass. If it is suspected or known that all or part of the drug was injected into the pocket during the refill procedure, monitor the patient closely for signs and symptoms of overdose in an appropriate facility for a sufficient amount of time or until the symptoms have resolved. Failure to recognize signs and symptoms and seek appropriate medical intervention can result in serious injury or death. Instruct patients to notify their healthcare professionals of the implanted pump before medical tests/procedures, to return for refills at prescribed times, to carry their Medtronic device identification card, to avoid manipulating the pump through the skin, to consult with their clinician if the pump alarms and before traveling or engaging in activities that can stress the infusion system or involve pressure or temperature changes. Strong sources of electromagnetic interference (EMI), such as short wave (RF) diathermy and MRI, can negatively interact with the pump and cause heating of the implanted pump, system damage, or changes in pump operation or flow rate, that can result in patient injury from tissue heating, additional surgical procedures, a return of underlying symptoms, and/or a clinically significant or fatal drug underdose or overdose. Avoid using shortwave (RF) diathermy within 30 cm of the pump or catheter. Effects of other types of diathermy (microwave, ultrasonic, etc.) on the pump are unknown. Drug infusion is suspended during MRI; for patients who can not safely tolerate diathermy and MRI, can negatively interact with the pump and cause heating of the implanted pump, system damage, or changes in pump operation or flow rate, that can result in patient injury from tissue heating, additional surgical procedures, a return of underlying symptoms, and/or a clinically significant or fatal drug underdose or overdose. Avoid using shortwave (RF) diathermy within 30 cm of the pump or catheter. Effects of other types of diathermy (microwave, ultrasonic, etc.) on the pump are unknown. Drug infusion is suspended during MRI; for patients who can not safely tolerate diathermy and MRI, can negatively interact with the pump and cause heating of the implanted pump, system damage, or changes in pump operation or flow rate, that can result in patient injury from tissue heating, additional surgical procedures, a return of underlying symptoms, and/or a clinically significant or fatal drug under- or overdose.

Infection; implant depth greater than 2.5 cm below skin; insufficient body size; spinal anomalies; drugs with preservatives, drug contraindications, drug formulations with pH ≤3, use of catheter access port (CAP) kit for refills or of refill kit for catheter access, blood sampling through CAP in vascular applications, use of Personal Therapy Manager to administer opioid to opioid-naive patients or to administer ziconotide.

Precautions:
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Adverse Events:
Include, but are not limited to, spinal/vascular procedure risks; infection; bleeding; tissue damage, damage to the system or loss of; or change in, therapy that may result in additional surgical procedures, a return of underlying symptoms, and/or a clinically significant or fatal drug underdose or overdose, due to end of device service life, failure of the catheter, pump or other system component, pump inversion, technical/programming errors, injection into the pocket or subcutaneous tissue or improper use, including use of non-indicated formulations and/or not using drugs or system in accordance with labeling; pocket seroma, hematoma, erosion, infection; post-lumbar puncture (spinal headache); CSF leak and rare central nervous system pressure-related problems; hygroma; radiculitis; arachnoiditis; spinal cord bleeding/damage; meningitis; neurological impairment (including paralysis) due to inflammatory mass; potential serious adverse effects from catheter fragments in intrathecal space, including potential to compromise antibiotic effectiveness for CSF infection; anesthesia complications, body rejection phenomena; local and systemic drug toxicity and related side effects; potential serious adverse effects from catheter placement in intravascular applications.

Adverse Events:
Include, but are not limited to, spinal/vascular procedure risks; infection; bleeding; tissue damage, damage to the system or loss of; or change in, therapy that may result in additional surgical procedures, a return of underlying symptoms, and/or a clinically significant or fatal drug underdose or overdose, due to end of device service life, failure of the catheter, pump or other system component, pump inversion, technical/programming errors, injection into the pocket or subcutaneous tissue or improper use, including use of non-indicated formulations and/or not using drugs or system in accordance with labeling; pocket seroma, hematoma, erosion, infection; post-lumbar puncture (spinal headache); CSF leak and rare central nervous system pressure-related problems; hygroma; radiculitis; arachnoiditis; spinal cord bleeding/damage; meningitis; neurological impairment (including paralysis) due to inflammatory mass; potential serious adverse effects from catheter fragments in intrathecal space, including potential to compromise antibiotic effectiveness for CSF infection; anesthesia complications, body rejection phenomena; local and systemic drug toxicity and related side effects; potential serious adverse effects from catheter placement in intravascular applications.

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