P990034

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Implantable Infusion Pump
Device Trade Name:	Medtronic® IsoMed® Constant Flow Infusion System Model 8472 IsoMed® Implantable Constant-Flow Infusion Pump Model 8543 IsoMed® Side Catheter Access Port Kit Model 8545 IsoMed® Side Catheter Access Port Kit Model 8553 IsoMed® Refill Kit Model 8555 IsoMed® Refill Kit
Applicant Name and Address:	Medtronic, Inc. 710 Medtronic Parkway NE Minneapolis MN 55432 USA
PMA Number:	P990034

Date of Notice of Approval to Applicant: JUL 21 2000

II. INDICATIONS FOR USE

The Medtronic® IsoMed® Constant Flow Infusion System (System) is indicated for use when patient therapy requires the chronic infusion of approved drugs or fluids. The drugs or fluids approved for use with the System and their applications include:

the chronic intrathecal infusion of preservative-free morphine sulfate sterile solution in the treatment of chronic intractable pain. A 0.9% solution of preservative-free Sodium Chloride Injection, USP, can be used to achieve the physician-prescribed concentration of preservative-free morphine sulfate sterile solution.

the chronic intravascular infusion of floxuridine (FUDR) for the treatment of primary or metastatic cancer. Bacteriostatic water, or physiological saline can be used to achieve the physician-prescribed concentration of chemotherapy drugs or to flush the pump reservoir. Saline or heparinized physiological saline (unless contraindicated) may be used during an interruption in chemotherapy to maintain catheter patency.

Refer to the appropriate drug labeling for a complete list of indications, contraindications, warnings, precautions, dosage and administration information, and screening procedures.

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III. DEVICE DESCRIPTION

The System consists of the Model 8472 IsoMed® Implantable Constant-Flow Infusion Pump (pump), and accessories consisting of the Models 8553 and 8555 IsoMed® Refill Kits, and Models 8543 and 8545 IsoMed® Catheter Access Port Kits. Use of the system requires selection of the appropriate pump reservoir size and flow rate, and catheter to provide a fluid pathway for drug administration to the intended site.

Pump

The pump is an implantable device that stores and delivers a constant flow of medication to a specific body site. The pump is disk-shaped with a diameter of 77 mm and an overall height of 24 - 37 mm, depending on reservoir size (see Figure 1 and Figure 2). A center reservoir access port and side catheter access port are located on the top of the pump and allow for percutaneous access to the pump reservoir and catheter, respectively, following implantation. A catheter port extends from the side of the pump to allow connection of the appropriate Medtronic® intraspinal or intravascular catheter. Four suture loops are spaced around the pump for fixation when implanted.

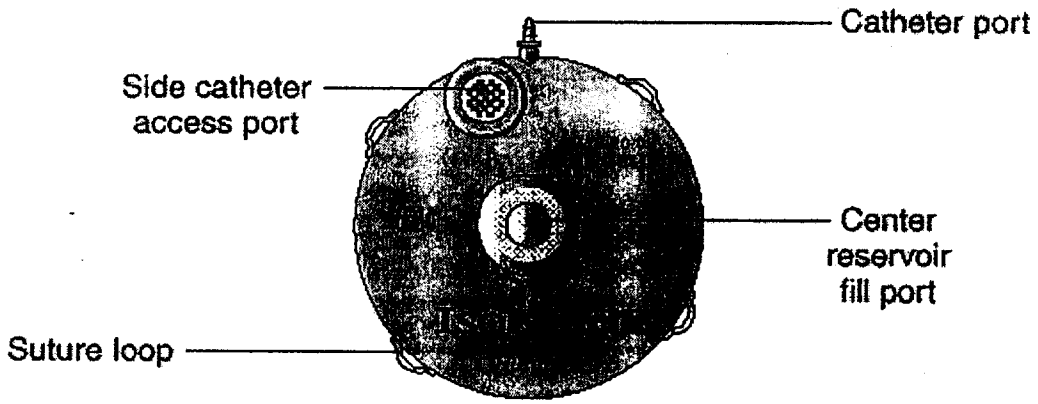

Figure 1. Pump - Top View

The pump is composed of the following components (refer to Figure 2):

Collapsible titanium reservoir (20 ml, 35 ml, or 60 ml)
Reservoir propellant (pump drive) chamber
Center reservoir fill port with self-sealing septum
Bacterial-retentive filter
X-ray identification tag
Side catheter access port with titanium screen and self-sealing septum
Titanium housing
Capillary tubing
Titanium suture loops

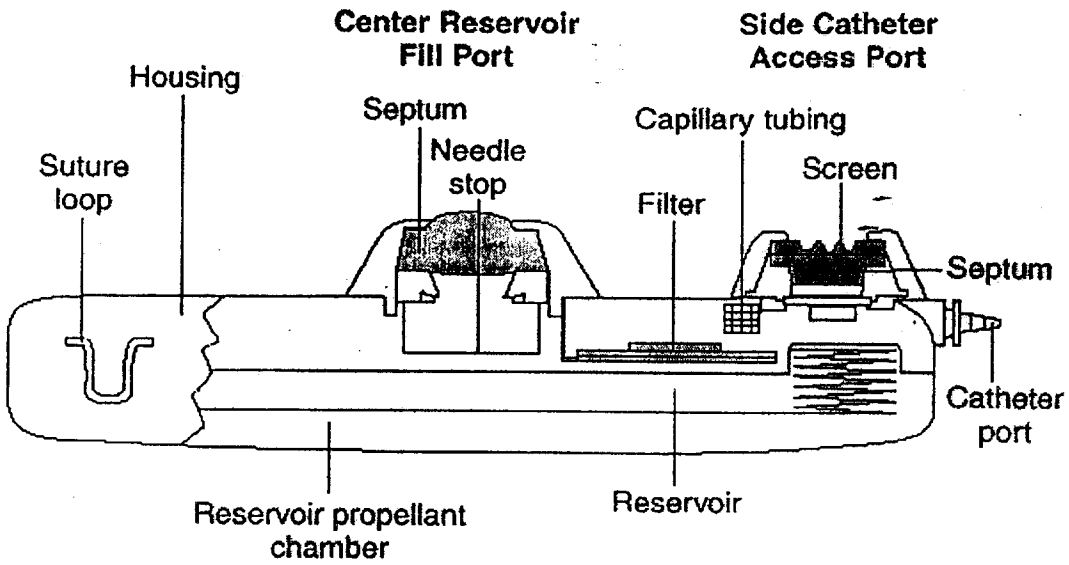

Figure 2. Cutaway View of Pump

The pump is available in three reservoir sizes, 20 ml, 35 ml, and 60 ml, and flow rates ranging from 0.3 ml/day to 4.0 ml/day. The complete range of pump models is provided in Table 1 below.

Table 1. Pump Model Numbers

Flow Rate	Reservoir Size (ml)		
(ml/day)	20	35	60
0.3	8472-20-03		
0.5	8472-20-05	8472-35-05	8472-60-05
1.0	8472-20-10	8472-35-10	8472-60-10
1.5	8472-20-15	8472-35-15	8472-60-15
2.0		8472-35-20	8472-60-20
2.5		8472-35-25	8472-60-25
3.0			8472-60-30
3.5			8472-60-35
4.0			8472-60-40

The physical specifications for the pump models are provided in Table 2 below.

Table 2. Pump Specifications

Parameter (max. values)	8472-20-xx	8472-35-xx	8472-60-xx
Reservoir Capacity	20 ml	35 ml	60 ml
Diameter	77 mm	77 mm	77 mm
Body Height	17 mm	22 mm	30 mm
Pump Height (Body + Septum)	24 mm	29 mm	37 mm
Weight	113 g	116 g	120 g
Displacement Volume	70 ml	101 ml	132 ml

The physical differences between the various pump models are limited to the overall height of the titanium shell and the length of the internal capillary tubing. All pump models use the same reservoir bellows. The maximum capacity of the reservoir is based on the limit of expansion due to the height of the pump's outer shell. The flow rate is varied by using different lengths of the flow restrictive capillary tubing. The flow rate is directly proportional to the length of the tubing, increasing the length increases the fluid flow restriction resulting in a slower flow rate, while decreasing the length reduces flow restriction and increases the flow rate.

The pump is separated into two chambers by a flexible titanium bellows. The outer chamber is a sealed compartment which contains a two-phase (liquid-vapor) propellant. The inner chamber is the drug reservoir. The vapor pressure of the propellant exerts pressure on the reservoir bellows forcing the drug from the reservoir through a bacterial retentive filter and capillary flow restrictor out of the pump and through a catheter to the intended site within the body.

Percutaneous access to the pump reservoir and the catheter are accomplished through separate silicone rubber septa using specific needles. The reservoir access (refill) septum is located in the center of the pump and is accessed using a 22 gauge non-coring needle. The catheter access port septum is located at the edge of the pump and has a titanium screen which limits access to 24 gauge (or smaller) non-coring needles. The screen prevents unintended access to the catheter when attempting to refill the pump which could cause a potentially harmful or lethal overdose. Use of the correct needle allows direct bolus infusion through the catheter via the catheter access port. The kits available for refilling the pump or accessing the catheter are described in the following section.

Accessories

The accessories to the pump are limited to the kits which provide the necessary components for refilling the pump and accessing the catheter via the catheter access port.

The Models 8553 and 8555 IsoMed® Refill Kits provide the components and instructions necessary to access the pump reservoir for emptying and filling the pump. The Model 8553 IsoMed® Refill Kit includes two 22-gauge non-coring refill needles

(1.5 and 2 inch lengths), an extension set with clamp and valved three-way connector, a 0.22 micron filter, 10cc filling syringe, 30cc emptying syringe, a fenestrated drape, and a refill template. The Model 8555 IsoMed® Refill Kit provides ten (10) sets of the those components required for refilling which are not normally in clinical inventories, each set contains two 22-gauge non-coring refill needles (1.5 and 2 inch lengths), an extension set with clamp and valved three-way connector, and a 0.22 micron filter.

The Models 8543 and 8545 IsoMed® Catheter Access Port Kits provide the components and instructions necessary to access the implanted catheter via the side catheter access port of the IsoMed pump. The Model 8543 IsoMed® Catheter Access Port Kit includes two 24-gauge non-coring refill needles (1.5 and 2 inch lengths), an extension set with clamp, a 0.22 micron filter, 10cc syringe, and a fenestrated drape. The Model 8545 IsoMed® Catheter Access Port Kit provides ten (10) sets of the those components required for catheter access which are not normally in clinical inventories, each set contains two 22-gauge non-coring refill needles (1.5 and 2 inch lengths), an extension set with clamp and valved three-way connector, and a 0.22 micron filter.

Catheters

The catheters intended for use with the pump are those commercially available Medtronic catheters currently labeled and approved for intraspinal or intravascular drug administration.

IV. CONTRAINDICATIONS

Implantation of this device is contraindicated in the presence of infection, when the pump cannot be implanted 1 inch (2.5 cm) or less from the surface of the skin, or in patients whose body size is not sufficient to accept the pump bulk and weight.
Blood sampling through the side catheter access port is contraindicated. The side catheter access port has not been tested for blood withdrawal.

Contraindications relating to the use of the prescribed drug must be observed.
FUDR should be used with added caution in patients with impaired hepatic or renal function.

Patients with known disease extending beyond an area capable of infusion should be considered for systemic therapy with other therapeutic agents.

V. WARNINGS

General

General Use - Improper use of implanted infusion pumps could result in drug under- or overdose. Users must comply with product instructions for initial preparation, implantation, initial filling, refilling, and injecting into the side catheter access port of the

pump. Technical errors may result in a return of underlying symptoms, drug withdrawal symptoms, or a clinically significant or fatal drug overdose.

Drug Removal - A significant amount of drug may be present in the pump reservoir, capillary tubing, side catheter access port, and catheter. Caution must be used to prevent drug overdose when accessing the side catheter access port or when changing concentrations or solutions in the pump reservoir.

To prevent drug overdose when accessing the side catheter access port, aspirate approximately 1 to 2 ml from the catheter to ensure drug removal unless contraindicated (e.g., vascular applications).

To prevent drug overdose when changing concentrations or solutions in the reservoir, always rinse the reservoir between solutions.

Drug Information/Labeling - Physicians prescribing the system must be familiar with the drug stability information listed in pump labeling and the indications, contraindications, warnings, and screening procedures described in the prescribed drug labeling.

Infusion Solution Calculation - Correct calculation of the infusion solution concentration is of critical importance in preventing over- or underinfusion.

Pump Overpressurization - Overpressurization of the pump reservoir can result in overinfusion, which can lead to a clinically significant or fatal drug overdose or cause damage to the pump.

Mixing Drugs - The effects of mixing drugs are unknown. Pump flow rate may decrease or stop if drug precipitation occurs.

Preimplant

Pump Packaging - Carefully examine the shipping package and sterile tray containing the pump (sterilization method: ethylene oxide gas). If the package is damaged, the sterile seal is broken, or the Use Before Date is past, do not implant or resterilize the pump.

Single Use Only - The pump is intended for Single Use Only - DO NOT REUSE.

Patient Information - During presurgical discussions, give the patient complete information concerning adverse events, emergency procedures, system complications or system failure, initial fill, refill and side catheter access port procedures, refill schedules, the consequences of "Twiddler's Syndrome" (manipulation of the pump through the skin), and the pump's weight and degree of protrusion.

Implant

Implanted Catheter Volume - During catheter placement, always determine the implanted catheter length, calculate the catheter volume, and record this information in the patient's medical record. The precise implanted catheter length, catheter model number, and pump

flow rate are of critical importance in calculating the time required for drug to advance to the catheter tip and in preventing a drug overdose when injecting into the side catheter access port.

Pump Replacement - During a pump revision that requires pump removal from the pocket and a fill procedure, always follow the instructions in the appropriate Medtronic refill kit (see the System Components Sheet packaged with the pump) for emptying and initial filling of the pump prior to replacing the pump in the pocket.

Components - The use of non-Medtronic components with this system can result in damage to Medtronic components, less than adequate therapy, or increased risks to the patient.

Implant Depth - Implant the pump 1 inch (2.5 cm) or less from the surface of the skin. Implantation depth of more than 1 inch can inhibit septum access.

Implant Location - Before closing the pocket, verify that after implantation the pump's center reservoir fill port and side catheter access port will be positioned away from the incision and easy to palpate, the catheter will not become twisted or contorted, and the catheter is secured well away from the center reservoir fill port and side catheter access port.

Postimplant

Pump Access - Improper injection through the side catheter access port or into the pump pocket can result in a clinically significant or fatal drug overdose. Refer to the pump labeling or the drug labeling for specific drug overdose symptoms and methods of management. To prevent drug overdose when filling the pump or when accessing the side catheter access port of the pump:

1. identify the pump model and reservoir volume;
2. identify the location of the center reservoir fill port and the side catheter access port;
3. use the appropriate Medtronic refill kit when refilling the pump and the appropriate Medtronic catheter access port kit when accessing the side catheter access port (see the System Components Sheet packaged with pump);
4. use the instructions, needles, and other accessories provided with the appropriate Medtronic refill kit (for filling the pump), or the instructions, needles, and other accessories provided with the Medtronic catheter access port kit (for accessing the side catheter access port) (see the System Components Sheet packaged with the pump); and
5. verify the location of the center reservoir fill port septum or the side catheter access port septum during needle insertion using other medical procedures as appropriate.

Contrast Media - When injecting contrast media into the intrathecal space via the side catheter access port, only use a contrast medium indicated for intrathecal administration.

Failure to use an indicated contrast medium may result in adverse events including but not limited to extreme pain, cramps, seizures, and death.

Injecting Drug - Do not inject drug directly into the catheter or through the side catheter access port to advance drug to the catheter tip; this can result in a clinically significant or fatal drug overdose.

VI. PRECAUTIONS

Qualifications

Implanting – The pumps must be implanted only by qualified physicians.
Preparing - Individuals trained in the operation and handling of the system must coordinate the preparation of the pump for implantation.

Prescribing - Physicians must understand the concentration, dose and rate relationships before prescribing the pump. Failure to understand these relationships can lead to drug under- or overdose.

Refilling - The pump must be refilled on a prescribed schedule only by qualified personnel. All refills must use the appropriate Medtronic refill kit and be in compliance with the procedures described in the appropriate Medtronic refill kit technical instructions (see the System Components Sheet packaged with the pump).

Accessing Side Catheter Access Port - Side catheter access port procedures must be conducted only by qualified personnel. All access into the side catheter access port must use the appropriate Medtronic side catheter access port kit and be in compliance with the procedures described in the appropriate Medtronic catheter access port kit technical instructions (see the System Components Sheet packaged with the pump).

Components - For a complete list of model numbers and components compatible with the pump, see the System Components Sheet packaged with the pump.

Storage and Handling

Storage Temperature - Do not expose the pump to temperatures above 110° F (43° C) or below 41° F (5° C).

Damage - Do not implant a pump that has been dropped onto a hard surface or shows signs of damage.

Sterilization - Do not steam autoclave or flash autoclave the pump prior to implant or following explant; the pump will explode at high temperatures.

Disposal - Do not incinerate the pump; explosion can result if the pump is subjected to incineration or cremation temperature. Return all explanted pumps to Medtronic for safe disposal.

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Preimplant

Physician Responsibility - The physician is responsible for choosing the surgical procedure, the techniques, and the intended therapy for the patient.

Nonfiltered Access Ports - Screening for drug response with implanted nonfiltered access ports is not recommended. For those patients who must be screened with such devices because of their medical condition, extreme care should be exercised to ensure that aseptic conditions are maintained.

General Pump Preparation and Implant

Antibiotics - Consider use of peri- and postoperative antibiotics for pump implantation and any subsequent surgical procedures.

Pump Operation - Do not implant the pump unless pump operation has been confirmed.
Catheter Connections - Make sure catheter placement and connections are secure. Failure to adequately connect, secure, and/or suture catheters can result in dislodgment, disconnection, cessation of therapy, or delivery of drug to the pocket or the subcutaneous tissue.

Reservoir Fill

Refill Kit - Always use the appropriate Medtronic refill kit when filling the pump reservoir (see the System Components Sheet packaged with the pump).

Needles - Always use the 22-gauge refill needles provided in the appropriate Medtronic refill kit when filling the pump reservoir. Use of other needles may prolong the procedure or damage the septum.

Connections - Prior to filling the pump, firmly tighten all extension tubing connections to prevent leaks.

Infection - If local or systemic infection is suspected, use extreme caution when emptying or refilling the reservoir.

Emptying Pump - Always empty the pump reservoir completely before filling with prescribed fluid. Use the 22-gauge refill needle and extension tubing set provided in the appropriate Medtronic refill kit for this procedure (see the System Components Sheet packaged with the pump). Filling a pump that has not been emptied completely may result in overpressurization.

Fill Volume - Do not exceed the reservoir volume when filling the reservoir. Overfilling the pump reservoir may result in overpressurization.

Reservoir Contents - The pump reservoir contents are under significant pressure. To prevent the reservoir contents from being ejected, do not use an open syringe when emptying the pump.

Side Catheter Access Port Access

Catheter Access Port Kit - Always use the appropriate Medtronic catheter access port kit when accessing the side catheter access port (see the System Components Sheet packaged with the pump).

Needles - Always use the 24-gauge needles provided in the appropriate Medtronic catheter access port kit when accessing the side catheter access port. Use of other needles may prolong the procedure or damage the septum.

Needle Damage - Use of excessive force inserting the needle into the center reservoir fill port may damage the needle tip.

Connections - Prior to accessing the side catheter access port, firmly tighten all extension tubing connections to prevent leaks.

Infection - If local or systemic infection is suspected, use extreme caution when accessing the side catheter access port.

Injection Rate - Do not exceed an injection rate of 5 ml per minute when accessing the side catheter access port.

24-gauge Needles - The side catheter access port is designed to allow entry of a 24-gauge (or smaller) needle.

Nonfiltered Access Port - The side catheter access port does not contain a bacterial-retentive filter.

Syringe Size - Do not overpressurize the side catheter access port when injecting fluids. Small syringes can generate very high fluid pressure. Except when clearing a catheter occlusion for vascular applications, syringes smaller than 10 ml should not be used for accessing the side catheter access port.

Injection Volume - Injection of more than 0.5 ml of fluid into the side catheter access port under high pressure may cause catheter disconnection or catheter damage and subsequent fluid leakage.

Intraspinal Applications

Solution - Use only preservative-free sterile solution for intraspinal applications.

Non-Therapy Periods - If therapy is discontinued for an extended period of time, it is recommended that the pump be filled with preservative-free sterile saline to maintain a patent fluid pathway. Refill as needed to ensure that the pump always contains fluid in the reservoir and pathway.

Contrast Media - Do not inject contrast media into the pump reservoir; this may impair pump operation.

Vascular Applications

Vesicant/Cytotoxic Drugs at Implant - If the drug to be used is a vesicant or has the potential to cause local tissue damage, do not put the drug into the pump until after implantation. Fill the pump and catheter with sterile saline (a heparinized solution may be used if not contraindicated) instead of the drug.

Anticoagulants - Physicians prescribing anticoagulant therapy to maintain vascular catheter patency must be familiar with the indications, contraindications, warnings, and dosage and administration information described in the drug labeling.

Non-Therapy Periods - During periods of non-therapy, the pump should be emptied of the drug and filled with sterile saline (a heparinized solution may be used if not contraindicated) to maintain vascular catheter patency. Refill as needed to ensure that the pump always contains fluid in the reservoir and pathway.

Catheter Flush - To maintain catheter patency, flush the catheter through the side catheter access port after every use and/or at a minimum of once per month if a non-heparinized solution is used in the reservoir.

Aspirating - Do not aspirate the catheter. If the presence of blood is suspected in the side catheter access port or catheter, flush the side catheter access port with a minimum of 10 ml of sterile saline (a heparinized solution may be used if not contraindicated).

Catheter Occlusions - Catheter occlusions may inhibit drug delivery.

Postimplant Clinician and Patient Information

CSF Leaks - Special procedures such as an abdominal binder, bed rest, or pressure dressing should be considered to prevent and reduce cerebrospinal fluid (CSF) leaks for those patients who are prone to CSF leaks.

Infection - Clinicians suspecting infection evidenced by, but not limited to, erythema, drainage, hyperemia, fever, swelling, and localized pain should perform appropriate diagnostic procedures and intervention.

Diathermy - Clinicians must avoid using diathermy near the implanted pump. Heat from diathermy may cause overinfusion.

Lithotripsy - Clinicians must avoid exposing the pump to lithotripsy. The effects of exposure to lithotripsy are unknown.

Aseptic Techniques - Clinicians must use strict aseptic technique during pump refill and side catheter access port procedures.

Implant Site - Clinicians and patients should keep the implant site clean, dry, and protected from external pressure or irritation.

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System Problems - Clinicians should contact Medtronic to evaluate and manage suspected system problems.

Inflammatory Mass - Clinicians and patients should be aware that in rare instances, the development of an inflammatory mass at the tip of the implanted intraspinal catheter may occur that can result in progressive clinical signs which bear monitoring. These signs include a progressive change in the character, quality, or intensity of pain; an increase in the level and degree of pain despite dose escalation; sensory changes (i.e., numbness, tingling, burning); hyperesthesia and/or hyperalgesia. Presentations that require immediate diagnosis include bowel and/or bladder dysfunction, myelopathy, conus syndrome, gait disturbances or difficulty ambulating, and paraparesis or paralysis. If the presence of an inflammatory mass is suspected, recommended evaluation should include a review of the patient history and neurological evaluation, radiological diagnostic procedures (such as MRI with contrast) and an appropriate clinical consultation.

Drug Information - Clinicians must notify patients of the appropriate warnings and precautions associated with the prescribed drug, including drug overdose and underdose signs and symptoms.

Refill Scheduling - Patients must return to the clinic or physician's office as scheduled to monitor system performance. Be aware that at refill the pump should contain at least 2 ml of fluid. The flow rate of the pump decreases rapidly and stops as the volume in the reservoir decreases from 2 ml to 0 ml. This can result in the potential loss of therapeutic effect or drug withdrawal symptoms.

Identification Card - Patients must carry their Medtronic Patient Identification Card at all times.

Travel Plans - Patients must notify their physician about extended travel plans so that pump refills or other procedures can be arranged.

Pressure and Temperature Changes - Patients must consult with their physician before engaging in activities involving pressure or temperature changes (e.g., scuba diving, saunas, heating pads placed over the pump site, hot tubs, hyperbaric chambers, long-duration flights, nonpressurized aircraft). Pressure and temperature changes can cause the pump to temporarily under- or overdispense the drug.

"Twiddler's Syndrome" - Patients must avoid "Twiddler's Syndrome" (manipulation of the pump through the skin), which can cause catheter disconnection, angulation, kinking, or dislodgment.

Unusual Symptoms - Patients must consult their physician if they notice any unusual symptoms or signs.

Physical Activities - Patients must avoid physical activities that may damage the implant site or device.

Personal Physicians - Patients must notify their personal and consulting physicians that they have an implanted pump.

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VII. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative practices to the use of an implanted pump for intraspinal or intra-vascular delivery of medication include:

Continuous or intermittent bolus percutaneous infusion of the prescribed drug intraspinally or intravascularly using an external pump.

Intermittent bolus injection of the prescribed drug intraspinally or vascularly using a needle and syringe.

VIII. MARKETING HISTORY

Since initial release in October 1997, over 1,200 pumps have been sold outside the United States, predominantly in Europe. The pump is currently approved for commercial distribution in Europe, Australia, Canada, Latin America, and Asia.

No significant adverse events related to the pump have been reported from outside of the United States.

IX. POTENTIAL ADVERSE EFFECTS

The adverse events associated with the use of this device may include, but may not be limited to, the following:-

Pump Complications

Cessation of therapy, due to random component failure, which may result in; return of underlying symptoms, drug withdrawal symptoms, or need for surgical removal of pump.

Change in flow performance characteristics, due to component failure, prolonged exposures to temperatures or pressures outside of normal exposures, or changes over time, which may result in; underinfusion of drug, return of underlying symptoms, drug withdrawal symptoms, overinfusion of drug, drug overdose, or need for surgical removal of pump.

Catheter Complications

Change in catheter performance, due to catheter kinking, catheter disconnection, catheter leakage, catheter breakage, complete or partial catheter occlusion, catheter dislodgment or migration, catheter fibrosis or hygroma, which may result in; delivery of drug into pocket or subcutaneous tissue, drug withdrawal symptoms, return of underlying symptoms, free-floating catheter in the CSF, underinfusion of the drug, CSF leak leading to spinal headache, CSF subcutaneous collection, or CNS pressure, related problems,

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damage to the spinal cord, hemorrhage, or need for surgical replacement/revision of catheter.

Drug Complications

Local and systemic drug toxicity and related side effects, complications due to using drugs not in accordance with the drug labeling, complications due to use of unapproved drugs with the system.

Procedural Complications

Surgical
Pump implanted upside down, pocket seroma, hematoma, erosion, or infection, CSF leak leading to spinal headache, CSF subcutaneous collection, or rare CNS pressure-related problems, radiculitis, arachnoiditis, bleeding, damage to the spinal cord, meningitis, spinal headache, medical complications, complications from anesthesia, damage to the pump, catheter, and catheter access system due to improper handling and filling before, during, or after implantation

Fill/Refill/Accessing Side Catheter Access Port
Infection, meningitis (in intrathecal applications), fill, refill, side catheter access port access error, which may lead to tissue damage or a clinically significant or fatal drug under- or overdose, or drug withdrawal, reservoir contamination, overpressurization of the reservoir, which can lead to a clinically significant or fatal drug overdose or damage to the pump, improper access through the side catheter access port, which can lead to a clinically significant or fatal drug overdose, injection into pocket or subcutaneous tissue.

Other
Body rejection phenomena, complications due to the interaction of the IsoMed Infusion System with unusual physiological variations in patients, surgical replacement of the pump or catheter due to any of the complications listed.

X. SUMMARY OF PRECLINICAL STUDIES

Nonclinical testing of the pump was conducted to ensure that the components and the finished device perform in accordance with the design specifications.

Component Qualification

Qualification testing confirmed the performance of the critical components of the pump including the refill and catheter access port septa, pump reservoir bellows, and the bioretentive filter. Puncture life testing of the refill and catheter access port septa demonstrated that use of the needles in the IsoMed® kits provided septa puncture life of 1,000 punctures for the refill septa and 500 punctures for the catheter access port septa. Life cycle testing of the drug reservoir confirmed that containment integrity would be maintained for a minimum of 1,000 cycles of filling and emptying. Testing of the filter

assembly confirmed a maximum pore size of 22 microns to provide bioretentive capability.

Pump Qualification

Flow accuracy testing under a variety of environmental and operational conditions was performed on 30 pumps. Nominal flow rate (37°C and reservoir at half capacity) was within ±10% of the labeled flow rate. The flow rate of the IsoMed pump over the entire operating range of temperatures (35-39°C), reservoir fill levels (full to near empty), and atmospheric pressures (0.85-1.05 bar) was within ±29% of the nominal flow rate.

Packaging Qualification

Qualification testing for the packaged product consisted of environmental stress tests including extreme temperature/humidity conditions, extreme vibration, stacking, and drop testing, as well as visual inspection and functional testing of sterile package seals and package materials and contents. All of the packages tested met the package design test requirements. The pumps were also directly exposed to extreme mechanical shock and vibration. Functionality of each device was verified at the completion of all tests.

Biocompatibility

The materials used in the pump that are directly exposed to body tissue and/or fluids are titanium and silicone rubber. These materials have been used in Medtronic implantable pumps and pacemakers for several years and have an established history of biocompatibility through long-term human use. Biocompatibility testing has also been performed on these materials. The materials passed the biocompatibility tests performed and are considered suitable for human implant.

Drug Compatibility and Stability Testing

The drug stability and compatibility testing performed in the pump in addition to the historical use and testing indicate that:

1. Preservative-free morphine sulfate is stable for a minimum of 90 days and is compatible for long term storage and delivery using the pump.

2. FUDR sterile solution is stable for a minimum of 27 days and is compatible for long term storage and delivery using the pump.

Electromagnetic Compatibility

The pump contains no electronic or ferromagnetic components that are susceptible to electromagnetic interference. Testing of the effects of exposure of the implanted pump to magnetic resonance (MR) fields of 1.5 T demonstrated performance within of the current guidance in regards to local specific absorption rate (SAR) and temperature

increases. Exposure resulted in no impact to pump performance and a limited effect on the quality of the diagnostic information

Hazard Analysis

Hazard analysis has been performed using failure modes and effects (FMEA) on the complete device and critical components. The hazard analysis was incorporated into design and development processes to ensure that critical failures modes or potentially hazard situations have been identified and adequately eliminated or mitigated. The FMEA process consisted of identification of potential failure modes and the possible effects of each failure mode on the safety and effectiveness of the device. Potential failure modes were ranked according to severity of the possible outcomes, likelihood of occurrence, and probability of detection. Finally, possible preventive actions were identified and actual actions taken to eliminate or mitigate the risks were determined.

Shelf Life

Sterile package and pump testing in addition to historical experience and product design considerations support a 24 month shelf life for the IsoMed pump.

Device Life

The life of the pump is determined by the life or viability of the two septa as such: 1,008 punctures of the refill septum or 500 punctures of the catheter access port septum (conservatively estimated as a minimum of 7 years of clinical use).

XI. SUMMARY OF CLINICAL STUDIES

Two multi-center, prospective open-label clinical studies of the pump were conducted in the United States . The clinical studies were designed to demonstrate that the pump accurately and safely delivers medications via intrathecal and intravascular routes of administration.

In addition to the two U.S. studies, a prospective open-label postmarketing outcomes study was conducted in Europe which provided supplemental evidence of the safety of the device and expanded information regarding therapeutic outcomes for intrathecal analgesic administration.

Study Overview

The primary objective of the U.S. clinical studies was to demonstrate that the pump effectively (accurately) delivers medications to the intended (intrathecal and intravascular) site(s). The accuracy endpoint was the clinically measured flow rate accuracy, defined as the ratio of the measured volume delivered to the expected volume delivered at pump refill:

$$\text{Clinically measured flow rate accuracy} = \frac{\text{Measured volume delivered}}{\text{Expected volume delivered}}$$

The secondary objective in both studies was to demonstrate the safety of the pump in the delivery of medications to the intended site(s) based on the serious adverse events associated with the pump and accessories. Events which resulted in an invasive intervention, death/disability, or a prolonged hospitalization were categorized as serious events.

The same statistical analysis methods was employed in both protocols for the same end points (i.e., accuracy and serious adverse events), which allowed the data from both studies to be "pooled" to demonstrate the performance of the device based on the combined data sets.

Intrathecal Study

The study was a non-randomized, prospective study of patients enrolled at 11 U.S. sites. The results analyzed to determine the effectiveness of the study was based on the 110 patients enrolled by February 2000. The results analyzed to determine the safety of the study was based on 173 patients enrolled by the end of the investigation. The following analysis addresses only effectiveness. Safety results are presented in Table 4 and Table 5.

Patients received intrathecal administration of analgesics for chronic, intractable pain. The average length of follow-up was 6.4 months (range 0.1 – 14.5 months), with a cumulative experience of 704.8 months.

Patients Studied
The patients, 58 female and 52 male, had an average age of 51 years (range of 26 – 88 years). One hundred and three (103) were enrolled with non-cancer pain, 7 had pain related to cancer or cancer-related treatment.

Methods
The primary objective of the study was to confirm that the average accuracy of the clinically measured flow rate (90% confidence limits) was within ±15% of the labeled flow rates. The patients had an average of 5.5 pump refills (range of 0 – 22 refills) with a total of 609 refills, 541 of which provided evaluable data.

The secondary objective was to demonstrate that the cumulative serious investigational device-related adverse event-free survival was greater than 85% (lower confidence interval) as confirmed from performance data evaluated at three month intervals.

Results
The intrathecal study results are summarized in Table 3. Four out of the 110 patients never received a refill, so the study results were based on the 106 patients with a total of 541 evaluable pump refills. The data demonstrated an average clinically measured flow rate accuracy of 99% (90% confidence interval of 96 – 100%). The serious adverse

event-free survival (related to the IsoMed pump and accessories) at 3 months was 100%. Please refer to the following sections in which adverse events are discussed.

Table 3. Intrathecal Study Results

Measure	Results	Experience	Patients (#)
Average clinically measured flow rate accuracy *[90% confidence interval]*	99% *[96 – 100%]*	541 pump refills	106
Serious adverse event-free survival at 3 months[a] *[estimated 90% confidence interval]*	100% *[96 – 100%]*	289.7 months	110

[a] Related to pump and accessories

Observed Adverse Events

Figure 3 and Table 4 and 5 provide additional details regarding the serious adverse device event experience reported during the study. This data is based on an expanded study group consisting of 173 patients with a cumulative experience of 1,327.2 months.

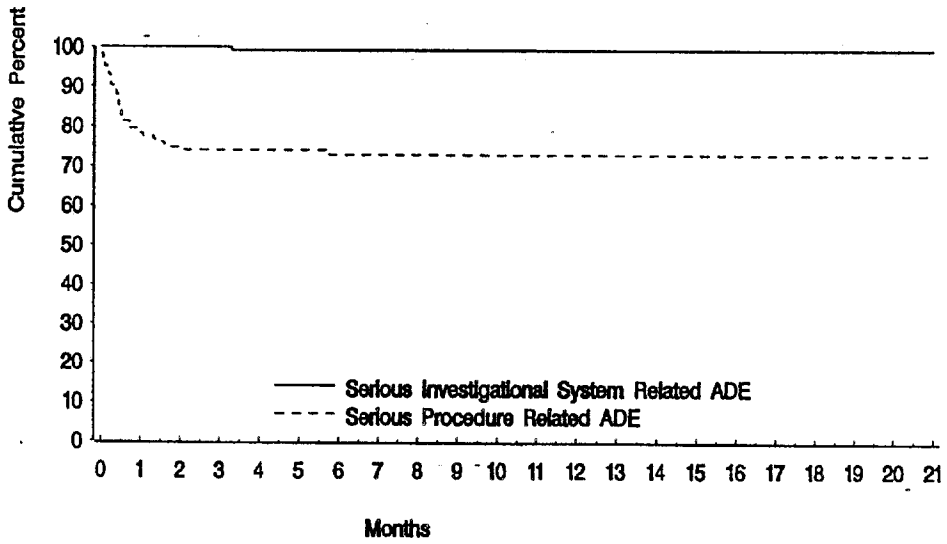

Figure 3. Cumulative Survival Curve Displaying Event-Free Survival for Serious Adverse Device Events (Intrathecal)

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Table 4. Serious[a] Adverse Event Summary (N = 173 patients)

Category / Adverse Event	Number of Events	Events per Patient Year	Number of Patients	Percent of Patients
SYSTEM-RELATED				
Unable to withdraw / inject into catheter access port	1	0.01	1	0.6%
PROCEDURE-RELATED[b]				
Implant				
Pocket hematoma/seroma	31	0.28	28	16.2%
CSF leak/accumulation	6	0.05	6	3.5%
Catheter cut/kink/dislodgment	4	0.04	4	2.3%
Pocket skin erosion/ wound dehiscence	4	0.04	4	2.3%
Pocket inflammation/ infection	3	0.03	3	1.7%
Explant				
Pocket hematoma/seroma	2	0.02	2	1.2%
CSF leak	2	0.02	2	1.2%

[a] Events that resulted in invasive intervention, death/disability, or hospitalization/prolonged hospitalization.

[b] Procedure-related ADE's with 2 or more occurrences observed in the study. Events that occurred only once are listed following the table.

Single Serious Adverse Events – (Procedure Related) Each of the following procedure-related serious adverse events were observed only once in the study: aseptic meningitis, gastrointestinal bleeding, incisional pain, local trauma to nerve root, oversedation/severe post-op pain, lack of drug effect, pump impinging on rib, seroma/CSF hygroma, and rash.

Table 5. Non-Serious Adverse Event Summary (N = 173 patients)

Category / Adverse Event	Number of Events	Events per Patient Year	Number of Patients	Percent of Patients
SYSTEM-RELATED				
Dull needle in refill kit	1	0.01	1	0.6%
PROCEDURE-RELATED[a]				
Post-surgical pain / discomfort	15	0.14	15	8.7%
CSF leak	3	0.03	3	1.7%
Pocket inflammation	3	0.03	3	1.7%
Lumbar infection/inflammation	2	0.02	2	1.2%
Fill / refill error	2	0.02	2	1.2%

[a] Procedure-related ADE's with 2 or more occurrences observed in the study. Events that occurred only once are listed following the table.

Single Non-Serious Adverse Events – (Procedure Related) Each of the following procedure-related, non-serious adverse events were observed only once in the study: paresthesia, migration, pump pocket hematoma/seroma, persistent headache, post-op

temperature, small defect at incision, upper respiratory infection, edema bilateral lower extremities, increased leg pain, rib soreness and dull refill needle.

Intravascular Study

The study was a non-randomized, prospective study of patients enrolled at 13 U.S. sites. The results analyzed to determine the effectiveness of the study was based on the 79 patients enrolled by February 2000. The results analyzed to determine the safety of the study was based on 188 patients enrolled by the end of the investigation. The following analysis addresses only effectiveness. Safety results are presented in Table 7 and Table 8.

Patients received intrahepatic arterial administration of chemotherapy for the treatment of primary or metastatic liver cancer. The average length of follow-up was 3.5 months (range 0.0 – 12.0 months), with a cumulative experience of 279.5 months.

Patients Studied
The patients, 49 male and 30 female, had an average age of 58 years (range of 23 – 83 years). Seventy five (75) were enrolled with colorectal cancer metastatic to the liver, 4 had other metastatic cancer.

Methods
The primary objective of the study was to confirm that the average accuracy of the clinically measured flow rate (90% confidence limits) was within ±15% of the labeled flow rates. The patients had an average of 6.2 pump refills (range of 0 – 25 refills) with a total of 487 refills, 419 of which provided evaluable data.

The secondary objective was to demonstrate that the cumulative serious investigational device-related adverse event-free survival was greater than 85% (lower confidence interval) as confirmed from performance data evaluated at three month intervals.

Results
The intravascular study results are summarized in Table 6. Twelve out of the 79 patients never received a refill, so the study results are based on the 67 patients with a total of 419 evaluable pump refills. The data demonstrated an average clinically measured flow rate accuracy ratio of 91% (90% confidence interval of 88 – 91%). When adjusted for the effects of the drug viscosity and arterial pressure (factor of 0.9026 based on the offset of the mean flow rates of the intrathecal and intravascular data) the average clinically measured flow rate accuracy is 101% (90% confidence interval of 98 – 101%). The serious adverse event-free survival (related to the pump and accessories) at 3 months was 100%.

Table 6. Intravascular Study Results

Measure	Results	Experience	Patients (#)
Average clinically measured flow rate accuracy ratio	91%	419 pump refills	67
[90% confidence interval]	*[88 – 91%]*		
Average clinically measured flow rate accuracy adjusted for drug viscosity/arterial pressure offset (0.9026)	101%	419 pump refills	67
[90% confidence interval]	*[98 – 101%]*		
Serious adverse event-free survival at 3 months[a]	100%	169.4 months	79
[estimated 90% confidence interval]	*[93 – 100%]*		

[a] Related to IsoMed pump and accessories

Observed Adverse Events

Figure 4 and Tables 7 and 8 provide additional details regarding the serious adverse device event experience reported during the study. This data is based on an expanded study group consisting of 188 patients with a cumulative experience of 602.2 months.

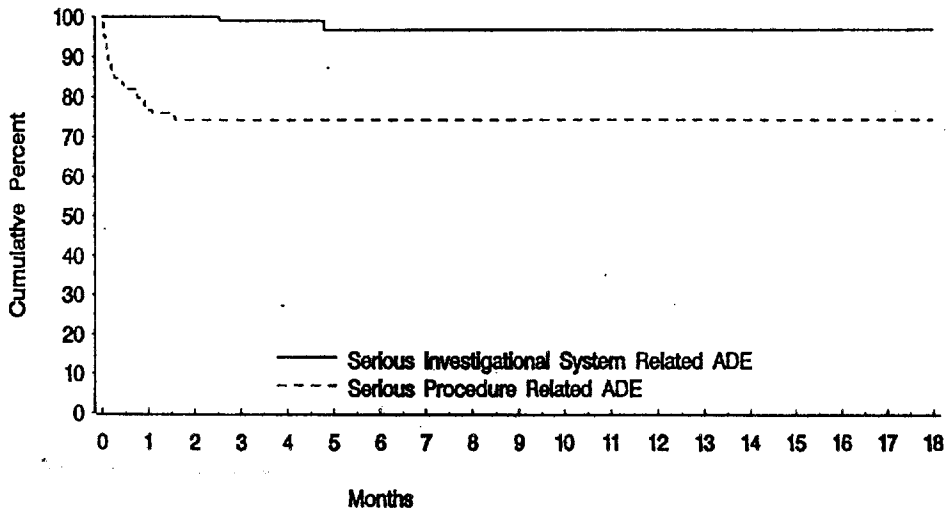

Figure 4. Cumulative Survival Curve Displaying Event-Free Survival for Serious Adverse Device Events (Intravascular)

Table 7. Serious[a] Adverse Event Summary (N = 188 patients)

Category / Adverse Event	Number of Events	Events per Patient Year	Number of Patients	Percent of Patients
SYSTEM-RELATED				
Underinfusion	1	0.02	1	0.5%
Pump inversion	1	0.02	1	0.5%
PROCEDURE-RELATED[b]				
Pump pocket hematoma/seroma	17	0.38	16	8.5%
Pump pocket infection	10	0.20	10	5.3%
Unable to enter catheter access port	4	0.08	3	1.6%
Extrahepatic misperfusion	3	0.06	3	1.6%

[a] Events that resulted in invasive intervention, death/disability, or hospitalization/prolonged hospitalization.

[b] Procedure-related ADE's with 2 or more occurrences observed in the study. Events that occurred only once are listed following the table.

Single Serious Adverse Events – (Procedure Related) Each of the following procedure-related serious adverse events were observed only once in the study: underinfusion, pump migration, pump inversion, difficulty accessing pump, inability to withdraw from or inject into catheter access port, perforated small bowel, collapsed lung post-op, liver abscess, midline incision infection, elevated bilirubin, pancreatitis, GI bleeding, fever/shortness of breath/wheezing, Pneumonia atelactasis, small bowel obstruction, post-op complications, and complications related to treatment of pulmonary embolus.

Table 8. Non-Serious Adverse Event Summary (N = 188 patients)

Category / Adverse Event	Number of Events	Events per Patient Year	Number of Patients	Percent of Patients
SYSTEM-RELATED				
Difficulty accessing/ entering reservoir	4	0.08	4	2.1%
Overinfusion	3	0.06	3	1.6%
Difficulty/pain during procedure	2	0.04	2	1.1%
Suture loop detached from pump	1	0.02	1	0.5%
Needle leak during refill	1	0.02	1	0.5%
Subcutaneous needle break	1	0.02	1	0.5%
Leakage at needle tubing junction _(catheter access port kit)	1	0.02	1	0.5%
PROCEDURE-RELATED[a]				
Pump pocket hematoma/seroma	8	0.16	7	3.7%
Post surgical pain	4	0.08	4	2.1%

Fever	4	0.08	4	2.1%
Pump pocket infection/inflammation	3	0.06	3	1.6%
Difficulty accessing reservoir or catheter access port	3	0.06	3	1.6%
Migration/inversion	2	0.04	2	1.1%
Increased bilirubin	2	0.04	2	1.1%
Incision drainage	2	0.04	2	1.1%
Constipation	2	0.04	2	1.1%

[a] Procedure-related ADE's with 2 or more occurrences observed in the study. Events that occurred only once are listed following the table.

Single Non-Serious Adverse Events– (Procedure Related) Each of the following procedure-related non-serious adverse events were observed only once in the study: urinary retention, hypotension, edema (RLQ), colored residual fluid, fill/refill error, pump pocket drug extravasation, elevated liver function tests, and rash.

Pooled Study Results

Pooling of the study data resulted in a total of 189 patients by February 2000, enrolled at 24 U.S. sites. The average length of follow-up for the pooled data was 5.2 months (range 0.0 – 14.5 months), with a cumulative experience of 984.3 months.

Patients Studied

The patients, 101 male and 88 female, had an average age of 51 years (range of 26 – 88 years). Table 9 provides a list of the pump models used in the studies.

Table 9. Pump Models Included in Clinical Studies

	Intrathecal Study		Intravascular Study		Combined	
Pump Model	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
8472-20-05	22	20.0%	--	--	22	11.6%
8472-20-10	--	--	4	5.1%	4	2.1%
8472-35-05	67	60.9%	--	--	67	35.4%
8472-35-10	9	8.2%	6	7.6%	15	7.9%
8472-35-15	1	0.9%	47	59.5%	48	25.4%
8472-60-15	11	10.0%	--	--	11	5.8%
8472-60-40	--	--	22	27.8%	22	11.6%
TOTAL	**110**	**100.0%**	**79**	**100.0%**	**189**	**100.0%**

Methods

Since the endpoints and analysis methods were the same for both studies, the data were pooled to provide results based on the combined experience. The flow rate accuracy data from the intrathecal and intravascular studies were pooled using the adjusted intravascular data set (0.9026 adjustment factor). The safety data was also pooled since pump implant technique and location, as well as clinician interaction were essentially the same for both studies.

Results

The pooled study results are detailed in Table 10. The pooled data demonstrated an average clinically measured flow rate accuracy of 100% (90% confidence interval of 97 – 100%). The serious adverse event-free survival (related to the pump and accessories) at 3 months was 100% (see Figure 5). With the exception of slightly elevated flow rates during the initial pump cycles, the average flow rates remained constant over time (see Figure 6).

Table 10. Pooled Study Results

Measure	Results	Experience	Patients (#)
Average clinically measured flow rate accuracy	100%	960 pump refills	173
[90% confidence interval]	*[97 – 100%]*		
Serious adverse event-free survival at 3 months[a]	100%	984.3 months	189
[estimated 90% confidence interval]	*[98 – 100%]*	459.1 months	

[a] Related to pump and accessories

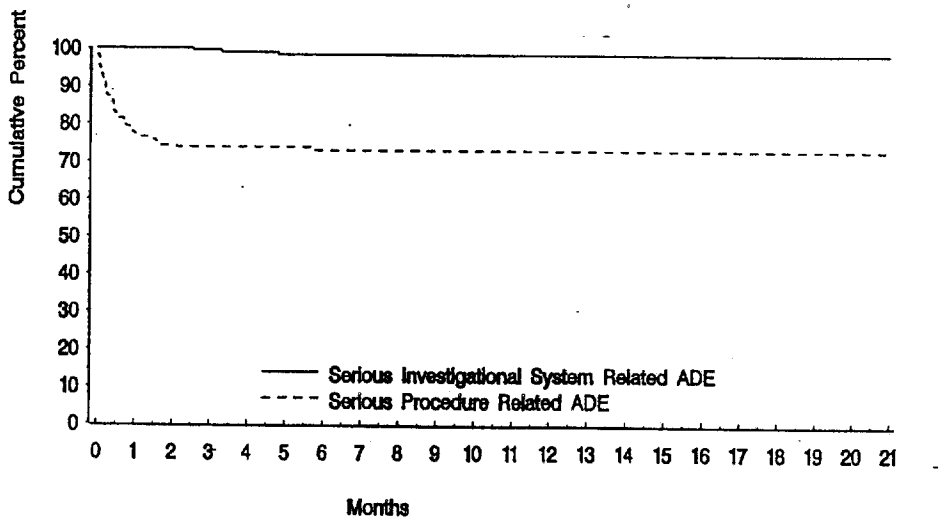

Figure 5. Cumulative Survival Curve Displaying Event-Free Survival for Serious Adverse Device Events (Pooled Data)

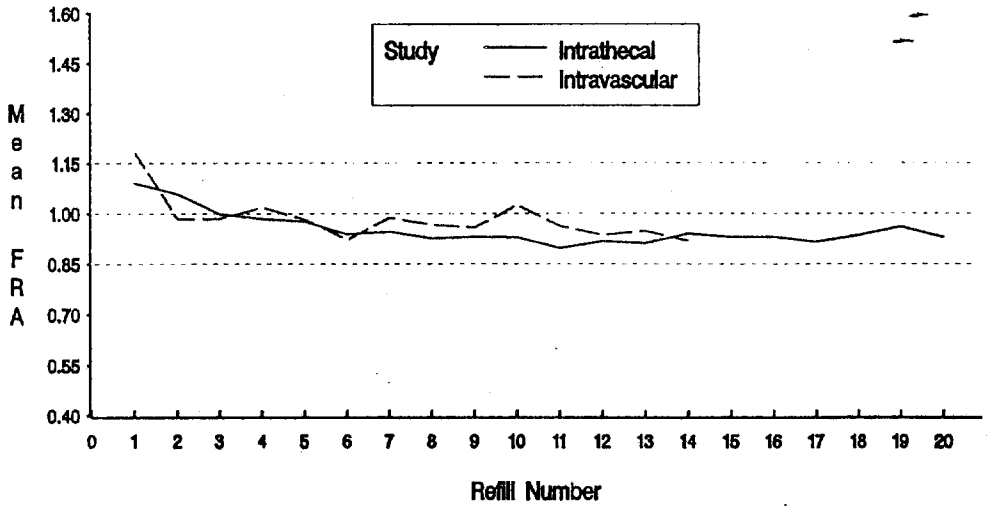

Figure 6. Average Flow Rate Accuracy Ratios for Pooled Data by Refill Number (Adjusted Intravascular Data, Minimum of 4 Refills)

European Outcomes Study

The study was a post approval non-randomized, prospective, open-label trial involving 76 patients enrolled at 17 European sites from October 1997 through February 1999. [The term, open label, refers to lack of specificity regarding the type of pain recorded or the particular analgesic infused.] Patients received intrathecal administration of analgesics (e.g., morphine hydrochloride, hydromorphone, bupivacaine, clonidine hydrochloride, etc.) for chronic, intractable pain. The average length of follow-up was 4.6 months (range 0 – 12.9 months), with a cumulative experience of 348 months.

As of the data cut-off date of February 1, 1999, of the 76 patients enrolled, 60 patients remained actively on study, 8 had completed the study, and 8 had been removed from the study, 4 due to patient death (none attributed to the device).

Patients Studied

The patients, 46 female and 30 male, had a mean age of 54 years (range of 20 – 84 years). Sixty eight (68) were enrolled with non-cancer pain, 8 had pain related to cancer or cancer-related treatment.

Methods

Data were collected at implant and at 3 months, 6 months and 12 months post implant to monitor device performance and safety, to collect outcome data and to determine clinical practices with the system.

The primary objective of the study was to compare pain relief at 6 months against baseline at implant as determined by Visual Analog Scale (VAS) and the Brief Pain Inventory (BPI) ratings.

Results

The four categories of the VAS (pain at its worst, pain at its least, pain on average, and pain right now) were all statistically significantly reduced at 6 months compared to baseline ($p<0.05$), see Figure 7. The quality of life measurements (general activity, mood, walking ability, normal work, relations with other people, sleep, enjoyment of life) of the Brief Pain Inventory were also statistically significantly improved at 6 months compared to baseline ($p<0.0001$), see Figure 8.

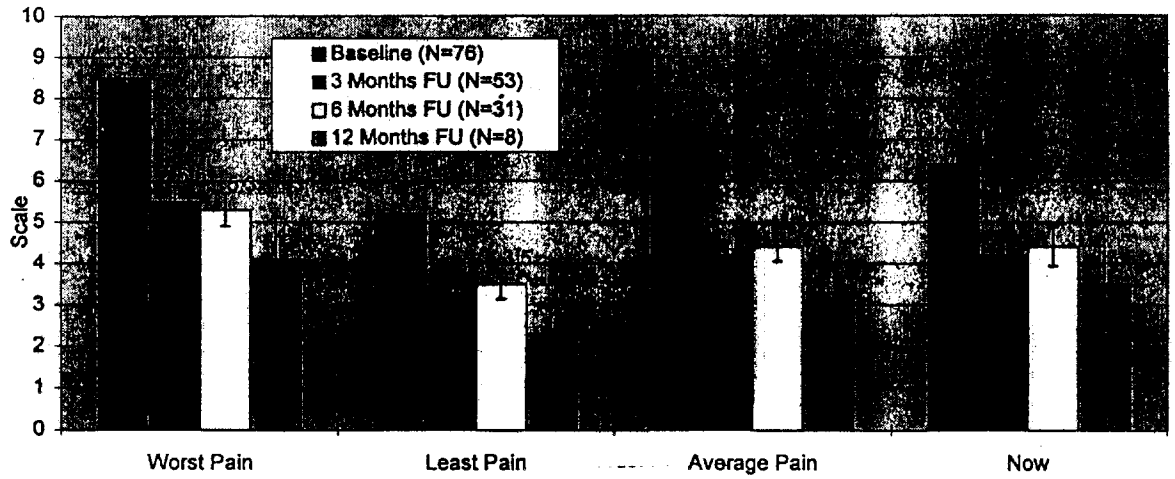

Figure 7. Visual Analog Scale Pain Ratings

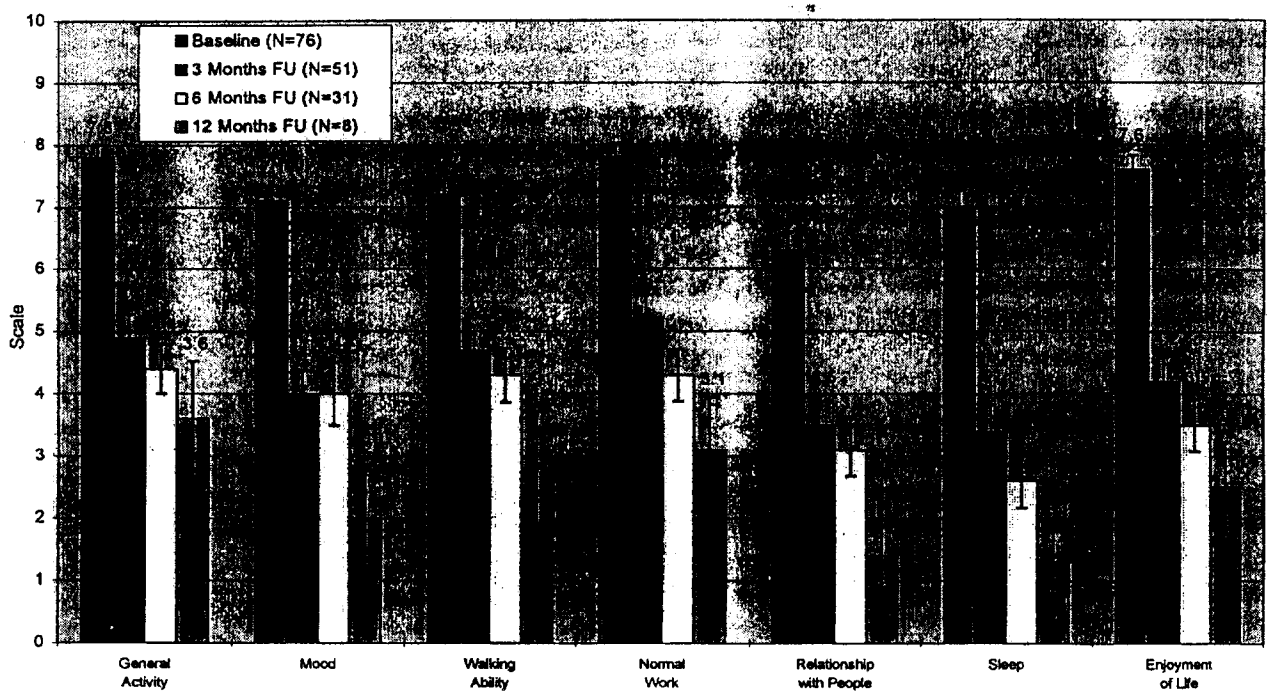

Figure 8. Brief Pain Inventory - Quality of Life Ratings

The types and rates of adverse events reported in the European study are very similar to those reported in the U.S. studies (see Table 11).

Table 11. Adverse Event Type (Outcomes Study)

Adverse Event	No. of Events	Events per Patient Year
Pocket hematoma/seroma	8	0.28
CSF leak	5	0.17
Spinal headache	4	0.14
Lack of/reduced pain relief	3	0.10
Pocket erosion/dehiscence	2	0.07
Incision infection	2	0.07
Catheter related	8	0.28
Other	12	0.41

Discussion and Conclusions

Clinical evaluation of the system focused on demonstration of the flow rate accuracy of the pump and the safety of the system when used for intrathecal and intravascular routes

of administration. Safety and effectiveness data from a total of 189 patients with 984 months of patient experience was collected under two IDE studies. Additional, nonpivotal outcome data was collected from 76 chronic pain patients with 348 patient months experience in Europe.

The flow rate accuracy of the pump as determined by clinical measurements closely matched the expected flow rates; the average accuracy was 99% (90% C.I.: 96 – 100%) of the expected flow rate in the intrathecal study, 91% (90% C.I.: 88 – 91%) in the intravascular study (101%, 90% C.I.: 98 – 101%, when adjusted for the effects of arterial pressure and drug viscosity), and 100% (90% C.I.: 97 – 100%) for the pooled data set. The flow rate accuracy remained constant over time. Analysis of the flow rate accuracy by models indicated no clinically significant differences due to reservoir size or flow rate of the pump.

No unanticipated adverse device effects or deaths attributed to the infusion system occurred during the studies. The adverse event profiles of the studies were similar. One serious adverse event related to the pump and accessories was reported in each IDE study consisting of an inability to withdraw CSF through the catheter access port in the intrathecal study where the clinician resorted to a lumbar puncture to obtain a CSF sample, and an inverted pump in the intravascular study requiring reopening of the pocket to reposition the pump.

The most frequently reported procedurally-related serious adverse events in the intrathecal study (= 2% of patients) were pump pocket hematoma/seroma, CSF leak/accumulation, catheter cut/kink/dislodgment, pocket erosion/wound dehiscence, and pocket inflammation/infection. Similarly, for the intravascular study the most common serious adverse events reported related to the implant procedure (= 2% of patients) were pump pocket hematoma/seroma, and pocket infection.

The results from the European outcomes study in intractable pain patients demonstrate that pain scores were significantly reduced and quality of life measures were significantly improved at 6 months post implant compared to those obtained prior to implant. The adverse events reported in the European study were similar in type and rate of occurrence to those reported in the U.S. studies.

Based on the results of the clinical investigations, Medtronic concludes that the system is safe and effective for intrathecal and intravascular routes of administration.

XII. CONCLUSIONS DRAWN FROM STUDIES

The non-clinical and clinical testing performed demonstrate a reasonable assurance that the system is safe and effective when used in accordance with the product labeling for:

1. the chronic intrathecal infusion of preservative-free morphine sulfate sterile solution in the treatment of chronic intractable pain, and

2. the chronic intravascular infusion of floxuridine (FUDR) for the treatment of primary or metastatic cancer.

XIII. PANEL RECOMMENDATIONS

The PMA was not referred to the General Hospital and Personal Use Devices Panel for review, because the Panel has previously reviewed similar information.

XIV. FDA DECISION

The sponsor agreed in writing to the general PMA "Conditions of Approval". There are no specific conditions of approval for this device.

FDA performed an inspection on March 29, 2000, and on the basis of the information reviewed, the sponsor has an acceptable GMP program.

CDRH issued an approval order for the stated indication for the applicant's PMA, P990034, on JUL 21 2000.

XV. APPROVAL SPECIFICATIONS

Directions for Use: Please see Final Draft Labeling (Please see Technical Manuals for pump, refill kits, and catheter access port kits.)

Hazards to Health from Use of the Device: Please see INDICATIONS, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, POTENTIAL RISKS, and ADVERSE EVENTS in the Final Draft Labeling.

Conditions of Approval: Please see Approval Order.