2012 Addendum to the Medtronic Neurostimulation & Intrathecal Drug Delivery Systems Product Performance Report:

Product Performance of SynchroMed II Pumps Exposed to On-Label and Off-Label Medications

Contact Information

We invite our customers to use this telephone number to call with suggestions, inquiries, or specific problems related to our products or the Product Performance Report.

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Purpose and Background

Purpose:

This document provides additional information and data to physicians following the "Urgent Medical Device Safety Notification: Use of Unapproved Drugs with the SynchroMed Implantable Infusion Pump" provided to healthcare professionals in November 2012. This document is in response to questions raised by health care practitioners following their receipt of the Medtronic Medical Device Safety Notification. This additional information is intended to guide clinical decision making related to long term use of medications delivered by the SynchroMed® II infusion system. The information provided in this addendum is subject to certain limitations which have been identified below.

This addendum contains information outside the FDA approved labeling for Medtronic's SynchroMed II Infusion System. It is recognized that healthcare providers prescribe FDA approved therapies to meet specific patient needs; however, Medtronic only directs the use of its products according to FDA approved labeling. Medtronic does not market its products for Off-Label indications and makes no representations regarding the efficacy for Off-Label uses. The information contained in this document is being disseminated with the sole intent of providing practitioners with the available data to make well informed medical decisions for their patients.

Background:

An analysis of Medtronic's prospective surveillance registry, the "Implantable Systems Performance Registry" (ISPR), was conducted to provide supplemental information to the Safety Notification letter sent in November 2012. There are over 300,000 SynchroMed systems (SynchroMed Classic, SynchroMed EL, and SynchroMed II) distributed globally to date. The ISPR systematically tracks device-related events and device-related reliability, incorporating data collected on >5000 SynchroMed II pumps at 50 clinical sites over the history of the registry. There are 26 active sites collecting data on intrathecal drug delivery systems in the ISPR study. The patient population at these study centers is similar to the general SynchroMed II population. The product performance report for the Implantable Systems Performance Registry is publicly available at: http://professional.medtronic.com/ppr/intrathecal-drug-delivery-systems/index.htm

As you review this information, please be advised that the use of Infumorph®, Prialt®, Lioresal® or Gablofen® are the only intrathecal FDA approved formulations for use with the Medtronic SynchroMed II Infusion System. Please be aware that the long term drug stability/compatibility and safety and/or efficacy of drugs not FDA approved for use with the SynchroMed II Infusion System has not been established.

Below please find a detailed summary of the supplemental information.

Study Design

- The registry is designed to track performance of Medtronic's implantable intrathecal drug delivery systems (infusion pumps and catheters).

- After enrollment and initial data collection, all patients were followed prospectively for adverse events for as long as patients are followed by the participating clinical center. Participating investigators reported patient symptoms and patient outcomes for each adverse event. Events were categorized as either product performance events or non-product performance events, where product performance events are considered pump failure when the pump was not performing according to specifications. Normal battery depletion was not considered a pump failure. Motor stall was defined as either a motor stall reported by the investigator or if motor corrosion was observed during the returned product analysis (regardless of motor function).

- Patient status updates were obtained every 6 months or until discontinuation of therapy or the patient was lost to follow up. Medications within the pump were recorded at each 6 month follow up. This provided a snap shot of medication use at these time points. The registry did not capture every medication or medication concentration used in the pump since any medication or concentration changes that occurred between follow-up visits were not recorded.

Pump Groups – ON/OFF-Label Categorization

Of the 5,062 SynchroMed II pumps enrolled into the ISPR through July 31, 2012, 4,828 had at least one available drug record. If a pump had no drug records in the ISPR, the pump was not classified, and was excluded from any analyses comparing On-Label to Off-Label. Pumps were categorized as being On- or Off-Label using the following criteria:

- On-Label: If a pump has at least one drug record in the ISPR, and none of the records show Off-Label drug exposure, that pump is considered On-Label even if the complete drug history of that pump is unknown.
  - For pumps used for pain patients, if the drug record has only one drug and it is morphine sulfate or ziconotide these pumps are considered On-Label.
  - For pumps used for spasticity patients, if the drug record has only one drug, and it is baclofen, that drug record is considered On-Label. Note: The classification was based on the name of the drug only, not the reported concentration of the drug.
  - Pumps with an On-Label drug history and currently containing preservative free water or preservative free saline, or if previously contained preservative free water/saline and currently containing on-label drug were considered On-Label.

- Off-Label: Any drugs not specified above within the approved indications are considered Off-Label. Additionally, any drug record with more than one drug at a time in the pump (admixture) is considered Off-Label.
  - If a pump had any known exposure to Off-Label drugs (i.e., the Off-Label data have been collected in the ISPR), that pump is considered Off-Label, regardless of the amount of exposure time.
  - If a pump is filled with a medication that was reported as compounded, that pump is considered Off-Label.

Data Analysis

- Data Interval: Database Open and Closure Dates: August 7, 2003 - July 31, 2012.

- Survival estimates for each 3-month interval were calculated using life-table methods (for more details, see the Medtronic Neuromodulation Product Performance Report). Statistical testing comparing survival curves was performed using a Cox proportional-hazards model, as this model allows for late entry into the survival curve (which the ISPR has for pumps that were implanted prior to subject enrollment in the study). Since the survival estimate may become very imprecise with small effective sample sizes, Medtronic Neuromodulation's ISPR truncates device survival curves when the effective sample size is less than 20 active devices. At this threshold, one device failure yields a 5% decrease in cumulative survival. Additionally, the standard error for this survival estimate is approximately 5% (depending on previous conditional survival estimates), with 95% confidence intervals of approximately ±10%. Overall, this large variability of 20% around the cumulative survival estimate would greatly reduce the precision for the point estimate.

- Pump survival from product performance-related events was calculated and compared for the following groups:
  - All pumps: On-Label vs. Off-Label Drugs (including All Indications)
  - Pain: On-Label vs. Off-Label Drugs (including All Pain)
  - Spasticity: On-Label vs. Off-Label Drugs (including All Spasticity)

  Additionally, the cumulative failure rate (i.e., the estimated probability that a pump will have a product performance-related event by a given time point) is presented in table and graph formats for each of the sub-groups listed above.

Results

- **Total Study Population:** A total of 1,744 SynchroMed II pumps were classified as On-Label where there was no evidence of Off-Label drug/admixture exposure. A total of 3,084 pumps were classified as Off-Label whereby there is evidence of pump exposure to an Off-Label drug/admixture. One pump was excluded from the age analysis due to a missing subject age; two pumps were excluded from the gender analysis due to missing subject gender.

Table 1. Demographic Table

Characteristic	On-Label N=1,744	Off-Label N=3,084
Age (years) at enrollment: Mean (SD)	42.6 (21.7)	56.6 (13.4)
Female: N (%)	864 (49.5%)	1,792 (58.2%)
Indication: N (Row %)		
Non-Malignant Pain	557 (21.5%)	2,038 (78.5%)
Malignant Pain	36 (3.9%)	899 (96.1%)
Spasticity	1,151 (89.8%)	131 (10.2%)
Multiple/Unknown	0 (0.0%)	16 (100.0%)

There were a total of 66 reported SynchroMed II pump failures (i.e., had a product performance event) during the study observation period. Nine pump failure events were reported as normal battery depletion, but had a returned product analysis observation of high battery resistance. For this analysis, these pumps were not considered failures because they represent normal implant duration ranging from 5.6–6.8 years with no associated physician or patient complaint. Of the remaining 57 SynchroMed II pump failures, 33 pumps were classified as pump failure due to motor stall (with or without documented motor corrosion). The remaining classified failures were due to premature battery depletion, inconsistent pump reservoir volume, pump under infusion and other non-conforming reasons.

For the 33 pump failures due to motor stall, 24 of the pumps were associated with the patient presenting clinical signs and symptoms of possible drug withdrawal or increasing pain or spasticity. The other nine pumps had no patient reported patient signs and symptoms associated with the event, but upon explant and analysis had evidence of a motor stall occurrence or a laboratory observation of motor gear corrosion. There were no issues reported when pumps were replaced and/or re-started, such as drug overdose. None of the pump failures resulted in patient death. Overall, the rate of pump failures in this cohort was 1.2% (57/4,828) at a median follow up of 17.2 months.

Table 2 presents SynchroMed II pump survival for the **entire population** and is stratified by On-Label pump group and Off-Label pump group. The cumulative survival curve of the SynchroMed II pump for the **entire population**, and stratified by On-Label or Off-Label pump group, is shown in Figure 1. Table 3 and Figure 2 present the complementary cumulative failure rate estimates (Failure=100% Survival), with the scale of Figure 2 expanded to more clearly show the differences between the groups. The table and graph depict the cumulative failure rate over time and estimate the risk of pump failure for specific implant durations (i.e. time period from pump implant). Overall, the pumps with known Off-Label drug exposure had a 2.3 times greater risk of failure than pumps with no known Off-Label drug exposure (p=0.0182).

Table 2. *Total* Study Population: Survival from product performance-related pump events for all indications, by On/Off-Label drug exposure for SynchroMed II pumps

Category	Time Interval	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	81 months
All Pumps	Survival	99.8%	99.5%	98.8%	97.8%	96.1%	94.4%	94.4%
	Number of Pumps	2,981	2,170	1,511	976	548	243	42
On-Label Drugs	Survival	100.0%	99.8%	99.1%	98.8%	97.6%	97.6%	97.6%[a]
	Number of Pumps	1,136	845	569	340	178	73	36
Off-Label Drugs	Survival	99.8%	99.3%	98.7%	97.2%	95.5%	93.0%	93.0%
	Number of Pumps	1,774	1,287	917	616	362	170	29

[a] Survival for On-Label SynchroMed II pumps through 78 months.

Figure 1. SynchroMed II Cumulative Survival (All Therapies)

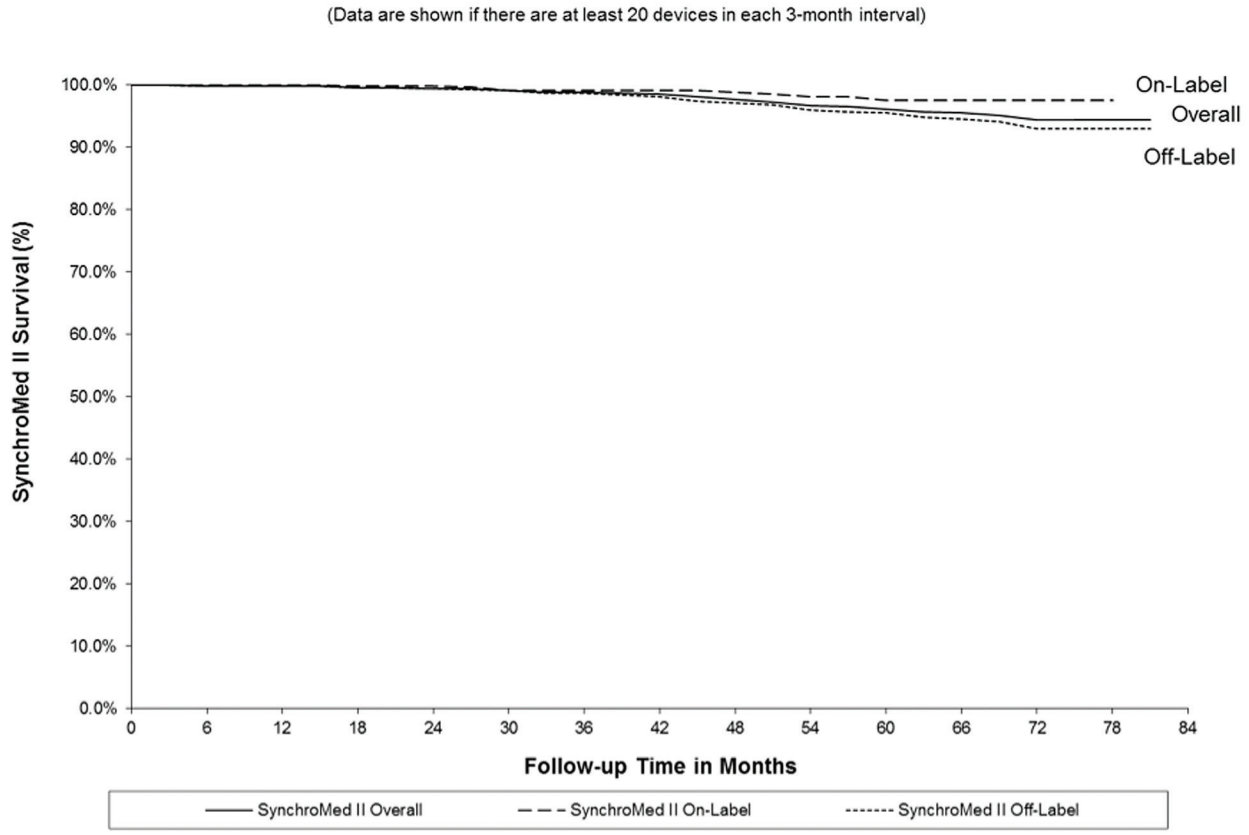
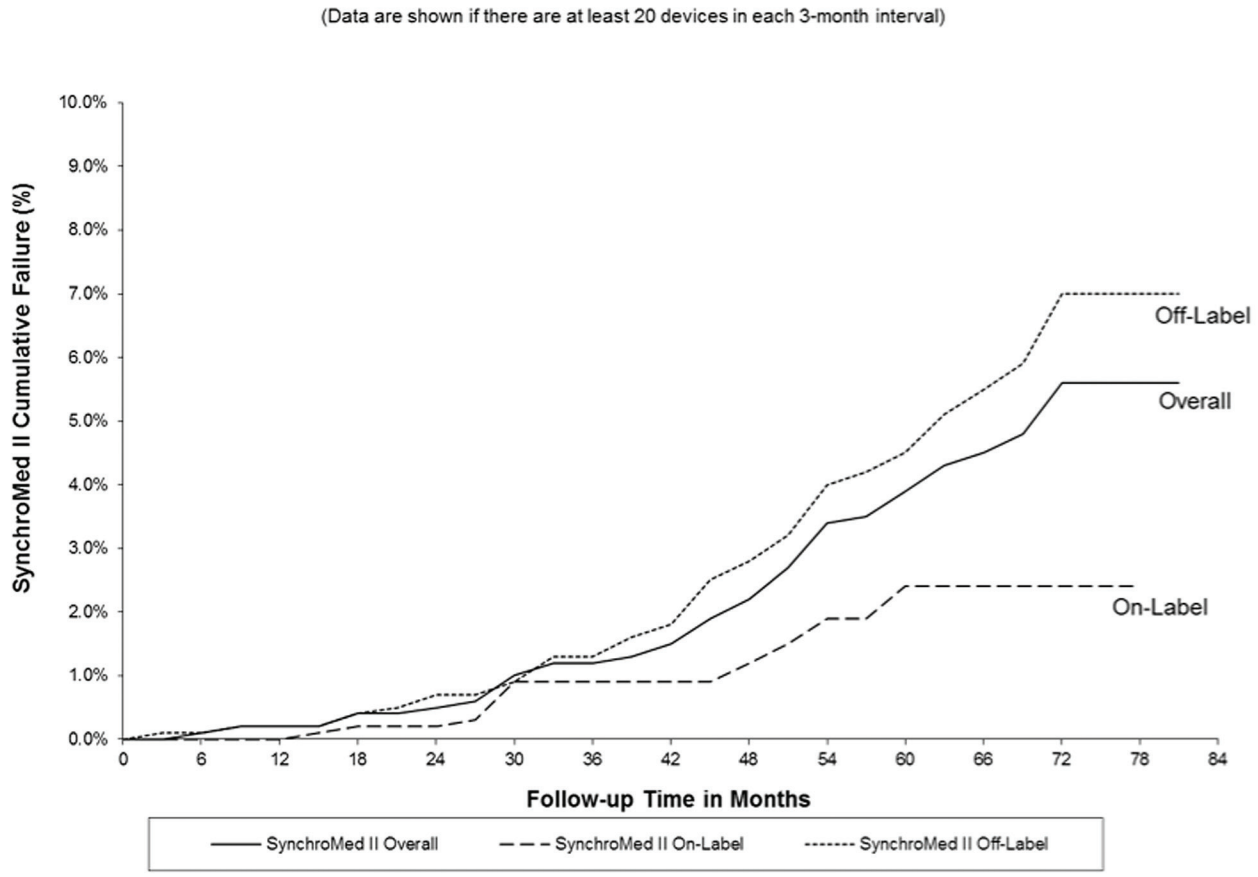


Table 3. *Total* Study Population: Cumulative failure of SynchroMed II pumps due to product performance-related pump events for all indications, by On/Off-Label drug exposure

Category	Time Interval	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	81 months
All Pumps	Failure	0.2%	0.5%	1.2%	2.2%	3.9%	5.6%	5.6%
	Number of Pumps	2,981	2,170	1,511	976	548	243	42
On-Label Drugs	Failure	0.0%	0.2%	0.9%	1.2%	2.4%	2.4%	2.4%[a]
	Number of Pumps	1,136	845	569	340	178	73	36
Off-Label Drugs	Failure	0.2%	0.7%	1.3%	2.8%	4.5%	7.0%	7.0%
	Number of Pumps	1,774	1,287	917	616	362	170	29

[a] Failure for On-Label SynchroMed II pumps through 78 months.

Figure 2. SynchroMed II Cumulative Failure (All Therapies)



- ***Pain Study Population:*** A total of 593 SynchroMed II pumps were classified as On-Label for pain therapy, where there was no evidence of Off-Label drug/admixture exposure. A total of 2,937 pumps were classified as Off-Label whereby there is evidence of pump exposure to an Off-Label pain drug/admixture. Table 4 presents SynchroMed II pump survival for the **Pain** indication and is stratified by On-Label pump group and Off-Label pump group. The cumulative survival of the SynchroMed II pump for the **Pain** indication,

and stratified by On-Label or Off-Label pump group, is shown in Figure 3. Table 5 and Figure 4 present the complementary cumulative failure rate estimates (Failure=100% Survival), with the scale of Figure 4 expanded to more clearly show the differences between the groups. The difference in survival between the On-Label and Off-Label groups for the pumps in the pain population was similar to what was observed for the entire population (all therapies). Statistical testing, however, was not performed due to low sample size in the On-Label group at the five year (60 month) follow up (n=20) and beyond.

Table 4. *Pain* Study Population: Survival from product performance-related pump events for Pain indication, by On/Off-Label drug exposure for SynchroMed II pumps

Category	Time Interval	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	81 months
Pain Overall	Survival	99.8%	99.3%	98.4%	97.0%	95.3%	92.8%	92.8%
	Number of Pumps	2,027	1,412	982	633	364	168	28
Pain On-Label	Survival	100.0%	99.3%	97.3%	97.3%	97.3%		
	Number of Pumps	328	198	119	51	20		
Pain Off-Label	Survival	99.8%	99.3%	98.6%	97.0%	95.2%	92.6%	92.6%
	Number of Pumps	1,674	1,208	862	581	344	160	26

Figure 3. SynchroMed II Cumulative Survival (Pain)

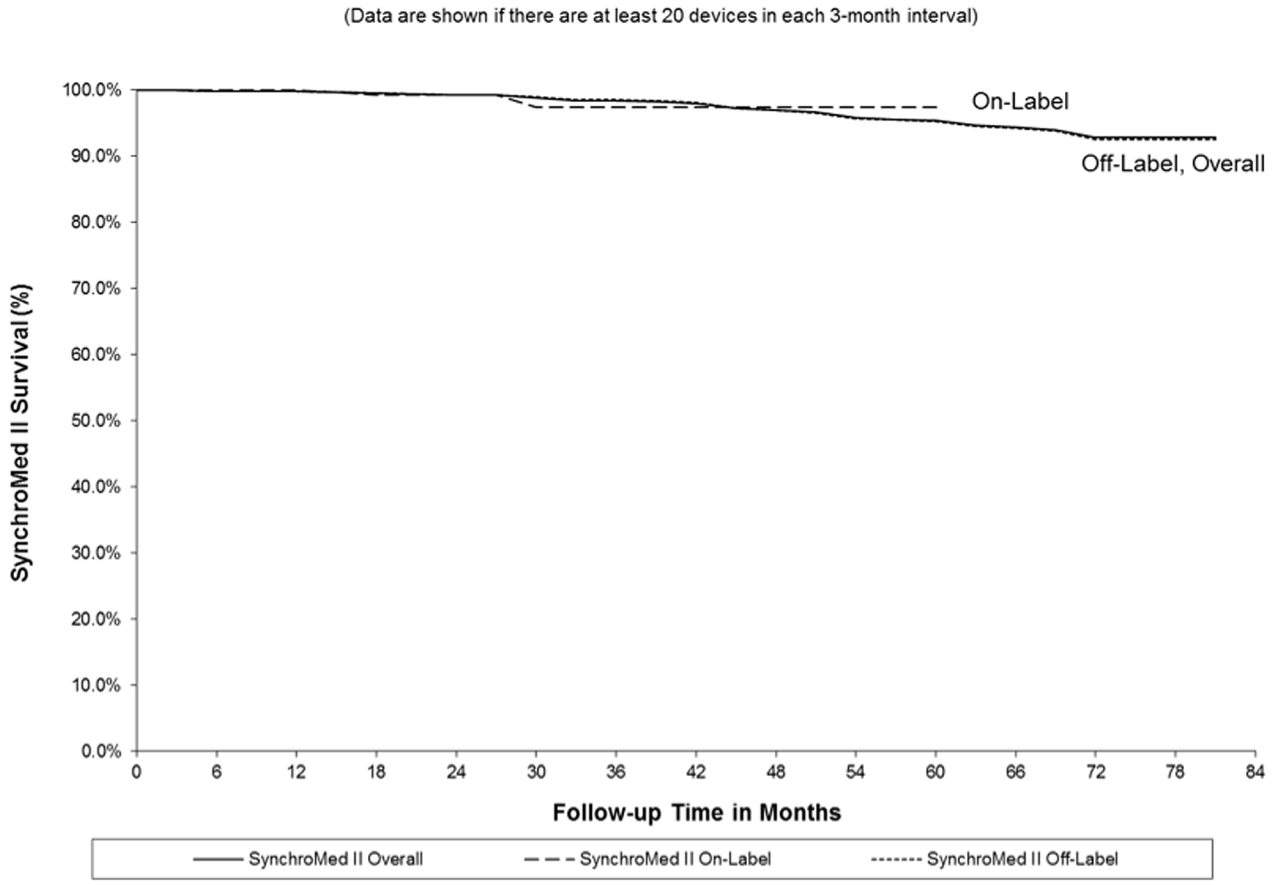
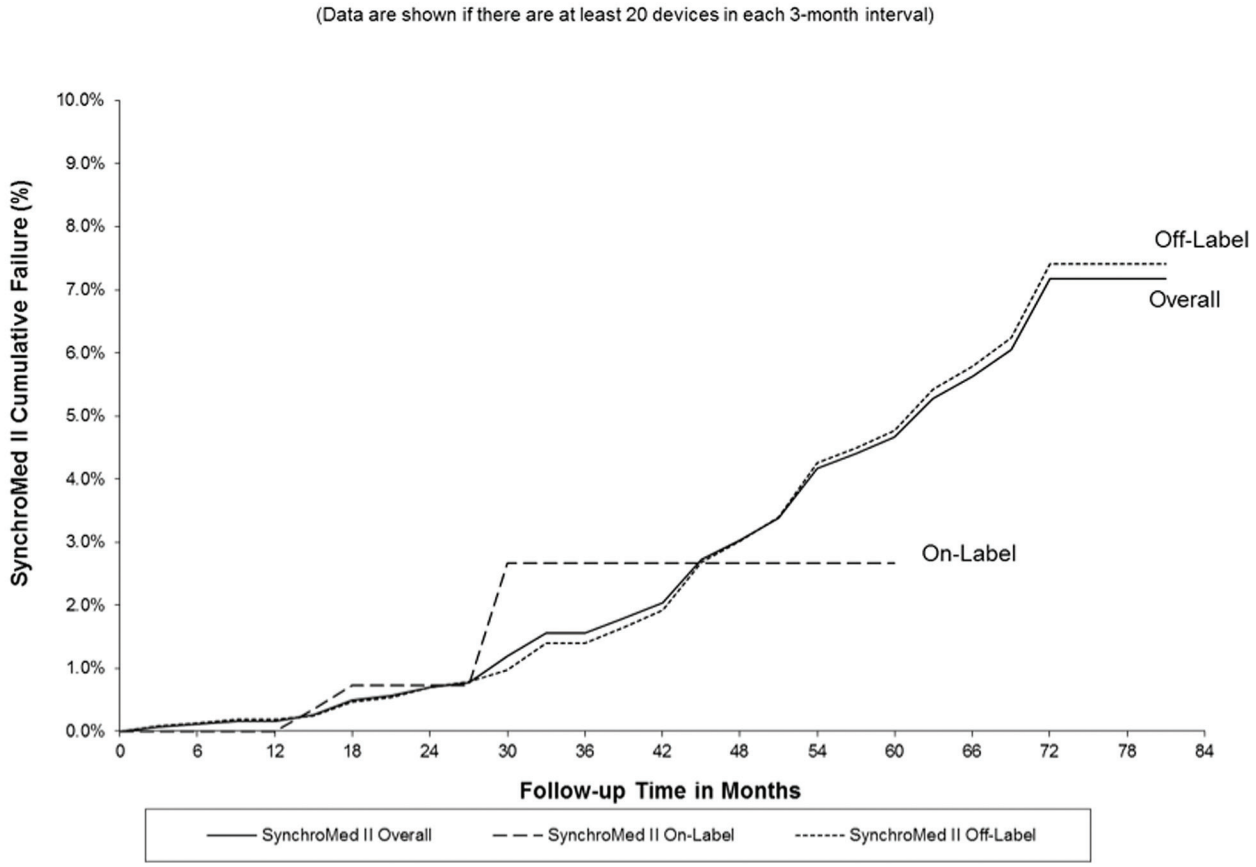


Table 5. *Pain* Study Population: Cumulative failure of SynchroMed II pumps due to product performance-related pump events for Pain indication, by On/Off-Label drug exposure

Category	Time Interval	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	81 months
Pain Overall	Failure	0.2%	0.7%	1.6%	3.0%	4.7%	7.2%	7.2%
	Number of Pumps	2,027	1,412	982	633	364	168	28
Pain On-Label	Failure	0.0%	0.7%	2.7%	2.7%	2.7%		
	Number of Pumps	328	198	119	51	20		
Pain Off-Label	Failure	0.2%	0.7%	1.4%	3.0%	4.8%	7.4%	7.4%
	Number of Pumps	1,674	1,208	862	581	344	160	26

Figure 4. SynchroMed II Cumulative Failure (Pain)



- ***Spasticity Study Population:*** A total of 1,151 SynchroMed II pumps were classified as On-Label for spasticity therapy, where there was no evidence of Off-Label drug/admixture exposure. A total of 131 pumps were classified as Off-Label whereby there is evidence of pump exposure to an Off-Label spasticity drug/admixture. Table 6 presents SynchroMed II pump survival for the **Spasticity** indication and is stratified by On-Label pump group and Off-Label pump group. The cumulative survival curve of the SynchroMed II pump for the **Spasticity** indication, and stratified by On-Label or Off-Label pump group, is shown in Figure 5.

Table 7 and Figure 6 present the complementary cumulative failure rate estimates (Failure=100%-Survival), with the scale of Figure 6 expanded to more clearly show the differences between the groups. Overall the survival for the On-Label pumps was similar to the entire pump population (all therapies). There were too few pumps in the Off-Label group to assess long term survival beyond four years (48 months). Statistical testing was not performed due to low sample size in the Off-Label group at the 48 month follow up (n=35) and beyond.

Table 6. *Spasticity* Study Population: Survival from product performance-related pump events for Spasticity indication, by On/Off-Label drug exposure for SynchroMed II pumps

Category	Time Interval	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	78 months
Spasticity Overall	Survival	99.8%	99.8%	99.5%	99.2%	97.6%	97.6%	97.6%
	Number of Pumps	951	757	529	343	183	75	38
Spasticity On-Label	Survival	100.0%	100.0%	99.7%	99.3%	97.9%	97.9%	97.9%
	Number of Pumps	808	647	450	289	158	65	32
Spasticity Off -Label	Survival	100.0%	100.0%	100.0%	100.0%	100.0%[a]		
	Number of Pumps	97	77	55	35	21		

[a] Survival for Off-Label SynchroMed II pumps (spasticity) through 57 months.

Figure 5. SynchroMed II Cumulative Survival (Spasticity)

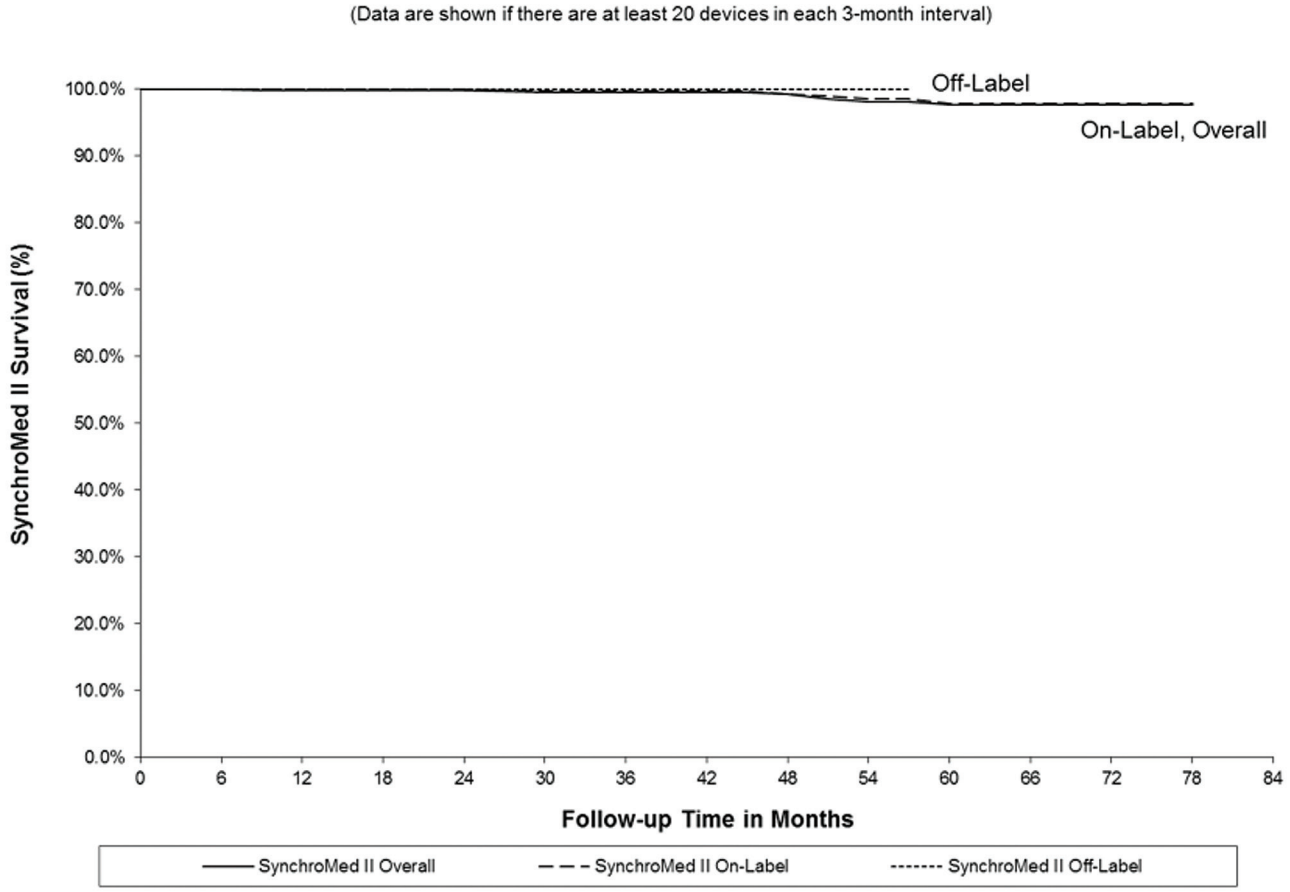
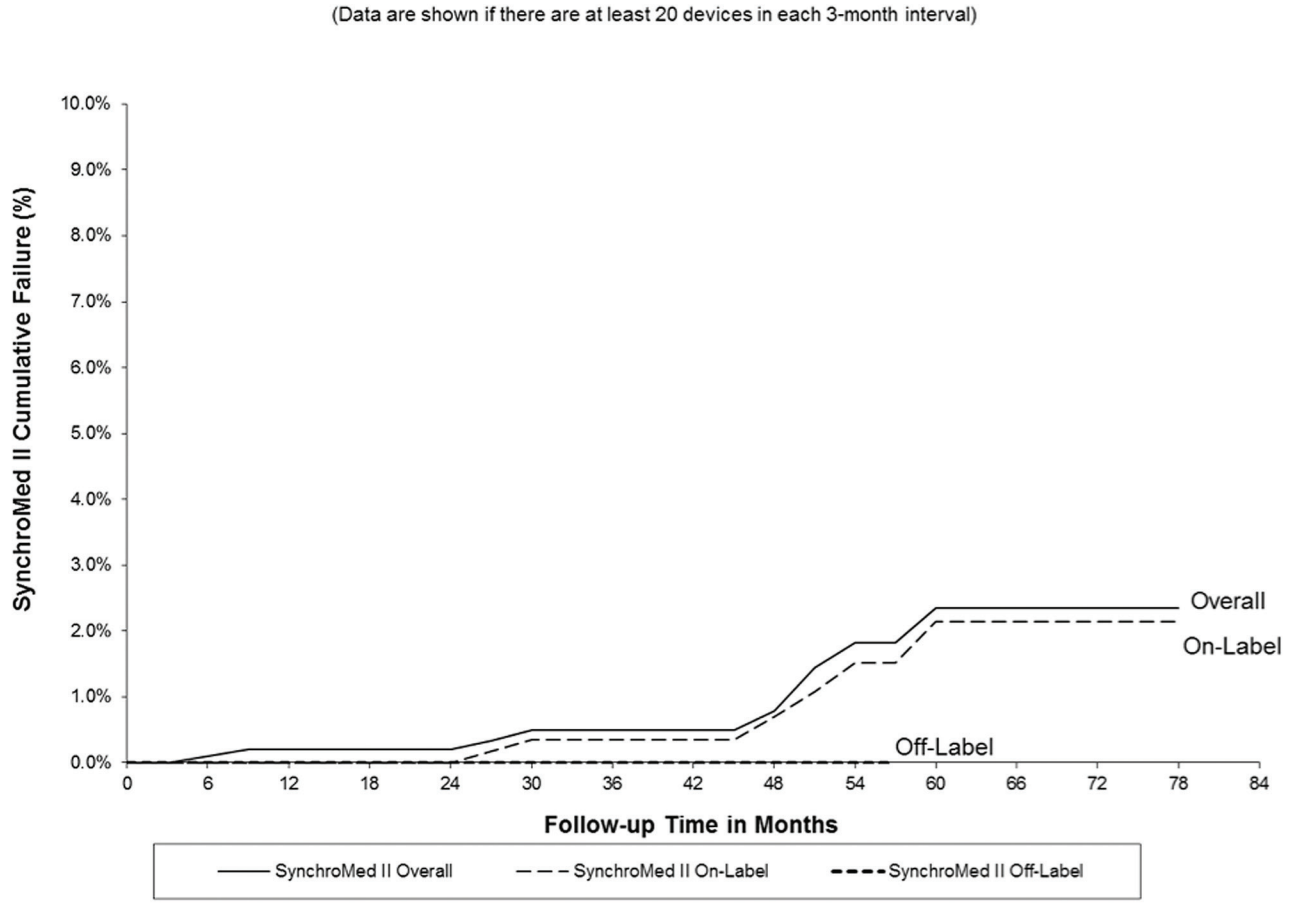


Table 7. *Spasticity* Study Population: Cumulative failure of SynchroMed II pumps due to product performance-related pump events for Spasticity indication, by On/Off-Label drug exposure

Category	Time Interval	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	78 months
Spasticity Overall	Failure	0.2%	0.2%	0.5%	0.8%	2.4%	2.4%	2.4%
	Number of Pumps	951	757	529	343	183	75	38
Spasticity On-Label	Failure	0.0%	0.0%	0.3%	0.7%	2.1%	2.1%	2.1%
	Number of Pumps	808	647	450	289	158	65	32
Spasticity Off -Label	Failure	0.0%	0.0%	0.0%	0.0%	0.0%[a]		
	Number of Pumps	97	77	55	35	21		

[a] Failure for Off-Label SynchroMed II pumps (spasticity) through 57 months.

Figure 6. SynchroMed II Cumulative Failure (Spasticity)



Summary and Limitations

- Pump failures have been observed in pumps with both On-Label and Off-Label medication use during the follow-up period.

- Off-Label medication exposure is associated with an overall 2.3 greater risk of pump failure compared to On-Label medication exposure for the entire pump population. The rate of pump failure accelerates in the Off-Label group after 36 months of follow up. At 78 months of follow-up, the survival from pump failure for On-Label pumps was 97.6%, compared to a survival of 93.0% for Off-Label pumps.

- The data represents reported ISPR experience with a median follow up time of 17.2 months. The longer term data is based on a lower number of pumps and is subject to change as more follow up data is obtained via the registry. Survival curve truncation or plateaus do not imply that the implanted devices will not be adversely impacted beyond the time points of the current data.

- The On-Label pump group consisted of 66% spasticity therapy (1,151 vs. 593: Spasticity versus Pain pumps respectively). On the other hand, Off-Label group consisted of 96% pain therapy (2,937 vs. 131: Pain vs. Spasticity pumps respectively).

- Medication use was recorded as a snapshot at the time of follow up. It is possible that some On-Label pumps received Off-Label medications in between 6-month follow up periods. In addition, it is possible that some pumps designated as On-Label received compounded formulation of an On-Label equivalent (i.e., Lioresal) but was not designated in the case reporting form.

- The time a pump was exposed to an Off-Label medication was not assessed. It is possible that some Off-Label pumps were exposed only for a brief time period (e.g., < 6 months).

- The risk of pump failure by type of drug was not assessed. Many Off-Label pumps received a multitude of medications over the pump life span. This limits the ability to associate a specific drug, drug concentration, or drug combination with increased pump failure risk.

Guidance Related to Monitoring for Pump Failure

- Pump failure may occur regardless of whether a medication is On-Label or Off-Label. Hence diligent pump monitoring practices should be employed to detect and/or preempt a potential motor stall and resultant pump failure. The following are monitoring recommendations:
  - Continue to monitor patients closely for the possible return of baseline symptoms. A return of baseline symptoms could potentially indicate pump damage.
  - Reinforce with patients and caregivers information on the signs and symptoms of withdrawal due to therapy cessation, and the importance of contacting their healthcare provider immediately if these signs and symptoms appear.
  - The SynchroMed II pump is designed with a critical alarm for pump motor stall. For patients implanted with a SynchroMed II pump, you can change the critical alarm interval frequency to sound every 10 minutes.
    - Remind patients, their caregivers, and your appropriate staff members to be alert for pump alarms.
    - At implant or follow-up visits, perform an alarm test to provide an opportunity for patients and caregivers to hear and differentiate between the critical and non-critical pump alarms.
    - For patients with a Personal Therapy Manager (PTM), the PTM will show alarm code 8476 if there is an active alarm when a bolus is attempted.
  - Retrieve logs when interrogating the SynchroMed II pump in order to check for motor stall events. Note that a temporary motor stall with recovery is expected behavior when the pump is exposed to a strong magnetic field such as during an MRI. Medtronic Technical Services can be contacted for further assistance evaluating motor stall events on logs.

- The use of Off-Label (unapproved drug formulations) may increase the risk of pump motor stall due to corrosion of the motor gears in the SynchroMed II infusion systems. Be aware that even if an On-Label medication (approved drug formulation) is currently being used, previous use of an Off-Label drug formulation in that pump could increase the risk of corrosion that may lead to a permanent motor stall and resultant pump failure.

- There are several physiochemical properties of Off-Label drugs that might increase the risk for pump damage resulting in motor stall and pump failure. Some factors that can increase the permeation rate of the corrosive agents in the drug formulation include hydrophobicity, degree of positive ionization, impurities, preservatives, pH adjustments, and concentration adjustments. Permeation of corrosive agents originating from many Off-Label drug formulations can occur at significantly higher rates than for On-Label drug formulations. Additives, Off-Label concentrations, and admixture solutions may alter the material properties of the infusion system components and exhibit chemical properties that are not compatible with the infusion system. This could interfere with the safe and reliable performance of the infusion system. Examples of these include:
  - Some antimicrobial preservatives and antioxidant preservatives are known to damage the SynchroMed infusion systems (i.e., sodium metabisulfite).
  - Drug concentrations that require additives to maintain solubility may not be compatible with the infusion system.
  - Admixture solutions may result in increased permeation rates of corrosive agents.
  - Drug formulations with a pH ≤ 3 are not compatible with the infusion system.
  - Higher permeation rates are generally associated with hydrophobic drugs (e.g., fentanyl, bupivacaine).