

December 13, 2018

Scott Gottlieb, MD
Commissioner
US Food and Drug Administration

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Nurse Consultant, Safety Signal Coordinator
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RE: Physician Guidance on the Use of Off Labeled Drugs in Intrathecal Drug Delivery Systems for Chronic Pain

Dear Dr. Gottlieb and Ms. White:

Recently the United States Food and Drug Administration (FDA) released a safety communication cautioning about the use of off-label drugs in intrathecal drug delivery systems (IDDS), or targeted drug delivery (TDD), for the treatment of chronic pain and spasticity. This action, intended to improve safety, has had and will have a detrimental impact on many patients and on the practice of medicine in the United States. This is particularly significant in that the great majority of patients implanted with IDDS are treated with off-label drugs or drug combinations making this the current standard of care in the United States^{1,2}.

The FDA is well aware that the general use of off-label medications has been an ongoing practice standard for many years, and has been a critical part of treating many medical conditions. Any communication which impedes the ability of physicians to successfully use intrathecal therapies in clinical practice could also have the unintended consequence of reversing the progress that has been made toward decreasing the use of high dose oral opioid medications. While we agree with the FDA's goal of improving safety and reducing risks, we also believe clarification is needed to protect patient safety and therapy access.

We do agree with the FDA that the use of labeled drugs should be considered as the first choice for use in these devices, and in the United States this would include Prialt (ziconotide), Infumorph (preservative free morphine sulfate) and baclofen¹. In the vast majority of patients, however, off-label medications are currently being used. Reasons for these current and historical practice standards are multidimensional but include those patients who failed on-label medications because of side effects or have had a poor response to treatment with lack of efficacy at reasonable dosing, while others cite a lack of commercially available concentrations and national drug availability.

Manufacturer registry data such as Medtronic's initiated Product Surveillance Registry (PSR, formerly called Implantable Systems Performance Registry, ISPR) for Targeted Drug Delivery (TDD) products (<http://professional.medtronic.com/ppr/index.htm>) shows that greater than 80 % of patients treated for chronic pain of noncancer origin receive drug(s) that are not currently approved in the United States for chronic intrathecal use³. Additionally, this number rises to greater than 90% in patients treated for cancer pain syndromes⁴.

Intrathecal drug delivery offers proven benefits over oral analgesics for the treatment of patients with chronic refractory pain as it delivers analgesic medications directly to the site of action, mostly on the dorsal horn of the spinal cord, thereby bypassing first pass metabolism and the blood brain barrier^{1,5}. Delivering medication directly to the nervous system, rather than through the systemic circulation, allows for analgesia at a lower effective dose and minimizes systemic side effects. After FDA approval of intrathecal drug delivery devices in the 1990s, physicians began to use intrathecal morphine for the salvage treatment of chronic pain patients. Over the ensuing years the practice became heterogeneous with drug selections becoming unpredictable once morphine failed to give relief, or caused intolerable side effects. Many novel agents, and drugs intended for other uses were used in humans causing unpredictable results and neurotoxicity. This led to a vacuum of guidance and a need for an algorithm for best practices in Intrathecal Drug Delivery. In this clinical and regulatory setting, international thought leaders developed a consensus group in 2000⁶.

The Polyanalgesic Consensus Conference (PACC) is an international multi-disciplinary body of pain treatment experts and was formed in 2000 to review evidence pertaining to the efficacy and safety of intrathecal therapy, and to provide guidelines regarding their use¹. This panel met in 2000, 2004, 2007, 2012, and 2017 to review current published data and current expert practice, with the goal of arriving at a living document and the generation of consensus publications to guide decision making regarding the appropriate candidates for intrathecal therapy, the appropriate medications starting doses and concentrations, and the management of devices used to deliver intrathecal therapy. The most recent PACC guidelines applied a validated evidence ranking system from the US Preventative Services Task Force (USPSTF) to establish the hierarchy of studies, along with degrees of recommendation and level of consensus. The panel's focus on safety, quality and efficacy and transparency has never changed over the past two decades. To that end, it has been unequivocally established that the standard of care for intrathecal therapy is to employ on-label and off-label medications.

In addition, some of the issues raised in the FDA communication should be clarified. Dosage errors are inaccurately linked to only non-FDA approved medications. These can occur when there is inadequate vigilance regarding ordering the drug, dosage entry and the subsequent programming of the intrathecal device. The PACC publications address the need for protocols to mitigate such errors. In addition, device malfunction can be directly related to intrathecal catheter granuloma from morphine even if used in the labeled fashion. This complication can be devastating, causing neurological injury and potential paraplegia. Pump failure with rotor malfunction and corrosion related to off-label use of medications was referenced in the FDA Safety Communications. In a registry specific to targeted drug delivery, 60 centers enrolled and included data for 7,459 patients with data collected between August 7, 2003 and July 31, 2016^{4,7}. A total of 2,330 programmable rotor pumps were classified as on-label, while a total of 5,189 pumps were classified as off-label with exposure to an off-label drug/admixture. Thus, 69 % of intrathecal pumps were exposed and used off-label drug/admixture. There was no statistically significant difference in the risk of failure between the on-label and off-label pumps implanted for the treatment of pain ($p=0.31$). Further, in a valve gated intrathecal pump post-marketing study, the majority of patients maintained on intrathecal therapy received off-label intrathecal medications⁸. Another valve gated intrathecal pump post-marketing study showed patients who received compounded vs commercially prepared intrathecal morphine showed improved efficacy and no difference in device-related failures, including pump failure and granuloma formation⁹. A recent poster presentation showed positive long-term outcome of intrathecal therapy in patients with refractory cancer pain using off label mixtures with no significant device failures over four years¹⁰. Other poster presentations on refractory cancer pain with intrathecal therapy using off-label medications such as hydromorphone, bupivacaine and clonidine show no evidence of device related failure including

granuloma formation^{11,12}. Notwithstanding, industry and physician commitment to reliable drug delivery was underscored by the improved safety and focus from the consent decree. Continued innovations and PACC reassessments highlight the importance of a strong patient-physician-industry-regulatory partnership.

The authors of the document strongly support the need for protecting patients and for FDA oversight to improve care. In this instance, we are concerned that this FDA alert may have the unintentional action of inappropriately limiting our ability to offer treatments within the standard of care for our chronic intractable pain patients. In this era of opioid misuse, overdose and death, it is even more important that the option of intrathecal drug delivery remains viable and continued communication be ongoing with the physicians who treat these intractable pain patients, the manufacturers of devices, and the FDA. In this spirit we would conclude with the following recommendations:

1. Intrathecal therapy is safe and efficacious in the treatment of chronic refractory pain in the cancer and noncancer patient populations.
2. When medically appropriate, physicians should consider use of on-label drugs in the treatment of chronic pain with intrathecal drug delivery devices. This is true in both the noncancer and cancer pain populations.
3. When side effects or loss of efficacy complicates the care of patients receiving intrathecal drug delivery systems, physicians are currently using off-label agents or adjuvants and this has been effective at safely helping these patients. This should be approached based on proper animal toxicity data, human studies of safety, or established track record of safety and efficacy in the medical literature.
4. Off label medications have been used safely for over 20 years and there is limited data to suggest off-label TDD medication use is unsafe.
5. When using intrathecal drug devices for the treatment of chronic pain patients, ongoing patient evaluation should occur with careful monitoring of side effects or complications. In the event of these adverse events, patient care should be immediately reassessed, and treatment modification should be carried out.
6. Physicians, manufacturers, and the FDA, should work together to assess additional labeling for drugs that are commonly used in clinical practice such as local anesthetics and alternative opioids. The presence of large device registries should allow for safety analysis that could be very helpful in giving improved guidance
7. An informed consent should include the risks and benefits and be provided to all patients receiving IDDS, including both on-label and off-label drugs.
8. Reporting of adverse events in this patient population should be transparent and timely. These adverse events should be carefully categorized and made available to physicians to assist in risk to benefit discussions and decision making.
9. FDA consider funding a prospective intrathecal drug delivery registry to track the safety and dosing with various intrathecal medications.

We recommend that we create a collaboration of physicians, medical societies, manufacturers, pharmacies, and the FDA to focus on this important issue. In that we request a meeting with the FDA to discuss the above issues and the need for the FDA to provide an addendum to their recent safety communication to recognize its inconsistency with current practice. The current communication places physicians at increased liability despite practicing within the standard of care. We look forward to collaborative discussions with the FDA to develop additional guidance for patients receiving IDDS in the United States.

Sincerely,

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