The National Parkinson Foundation's Helpline Speaks:

Lessons from the 2011 Sinemet Shortage

NATIONAL PARKINSON FOUNDATION

Find Answers. Change Lives. Beat Parkinson's.

Michael Rosenblatt, M.D.
Executive Vice President
Chief Medical Officer

Merck & Co., Inc.
WS3A-20
One Merck Drive
P. O. Box 100
Whitehouse Station, NJ 08889
michael.rosenblatt@merck.com
Tel 908 423 6446
Fax 908 423 1447

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Joyce Oberdorf
President & Chief Executive Officer
National Parkinson Foundation
1501 N.W. 9th Avenue / Bob Hope Road
Miami, FL 33136-1494

Dear Ms. Oberdorf,

I'm writing on behalf of Merck to share our comments on the paper about the past worldwide shortage of SINEMET® (carbidopa-levodopa) and SINEMET CR® (carbidopa-levodopa controlled release tablets), the medicine we have made for 40 years for the treatment of Parkinson's disease.

Thank you for providing important insights and capturing lessons learned from the supply shortage – what worked, and more importantly, what we as a company can do to better inform and guide patients in what can be a difficult and stressful situation. Chief among the lessons learned for Merck is the need for clearer, more timely communications to organizations such as yours that can help reach patients and caregivers to clarify the situation in an effective manner.

We are a company committed to developing innovations that address important medical needs, including Parkinson's and other neurodegenerative diseases, and to making sure our discoveries reach people who can benefit from them. Accordingly, we look forward to collaborating closely with the broad Parkinson's community.

We are sorry for any distress or inconvenience that the past supply shortage caused our patients and customers who rely on SINEMET. Please know that we appreciate the opportunity to collaborate with the National Parkinson Foundation as you continue your critical work as a strong voice for patients with Parkinson's and their caregivers.

Sincerely,

Michael Rosenblatt

Michael Rosenblatt, M.D.

Introduction

In 2010 and 2011, while transitioning Sinemet, the branded version of carbidopa/levodopa, in the United States from being manufactured by Merck & Company, Inc. (Merck) to Mylan Pharmaceuticals, Inc. (Mylan), and then transitioning the marketing of Sinemet from Bristol Myers Squibb to Merck, there was a period where both formulations (immediate release and controlled release), and all dosages were unavailable to Parkinson's disease (PD) patients. Shortages were experienced around the world, and patients were distressed and angry to lose access. To switch to a new formulation, many patients faced weeks of titration and detailed consultation with their neurologists.

Levodopa and the carbidopa/levodopa formulation in which it is widely distributed has been the gold standard for the care of Parkinson's disease patient since the late 1960's. In 1959, Arvid Carlsson speculated that Parkinson's disease (PD) was related to dopamine—work for which he won the 2001 Nobel Prize in medicine—and in 1960 Oleh Hornykiewicz confirmed Carlsson's work, and began to test levodopa as a potential therapy for PD. Later in 1967 George Cotzias demonstrated the benefit of dopamine replacement therapy in PD. By 1971, Victor Lotti of Merck, based at that time in West Point, Pennsylvania, added the important observation that levodopa in combination with carbidopa (which peripherally blocks dopa decarboxylase and allows L-Dopa to cross the blood brain barrier) provided a safe and tolerable formulation for PD patients, and it alleviated the most disabling and dose-limiting symptom from dopamine administration, nausea. Merck manufactured the drug and later sold under the brand name Sinemet (latin deribation- without emesis) until 2010, when, for business reasons, Merck transitioned the manufacture of some ingredients to Mylan Pharmaceuticals.

Levodopa remains the most important medication for the treatment of PD. The National Parkinson Foundation's (NPF) Quality Improvement Database (QII), a longitudinal study of the therapies for patients across the spectrum of disease (from very early to late disease) revealed that 89% of all people with PD are taking levodopa. This number approaches 100% as disease duration increases. The other medications were not even close in terms of usage: (dopamine agonists were used by 51%, a MAO-B inhibitor by 50%, and some form of antidepressant by 33%;

other medications had lower prevelance). Sinemet is the original brand for carbidopa/levodopa, and in his *Parkinson's Disease Treatment Guide*, Eric Ahlskog wrote that Sinemet, "generic formulations… are substantially less expensive," but that the physician may "stipulate brand-name if the patient reports better results with that formulation."

When the brand Sinemet shortage occurred in early 2011, this triggered a concern across the PD community. Below we will review the issues that led to concern about removal of brand drug, the patient concerns during the shortage, and during the recent introduction of the new Mylan-manufactured Sinemet formulation (Mylan Sinemet). All data is from the NPF Helpline project.

Issues with Generic Substitution

Since its launch in 2010, the National Parkinson Foundation Helpline has received many calls from patients looking for information about generic substitution, and also documented an expressed dissatisfaction with generic carbidopa/levodopa when compared to Merck-manufactured Sinemet (Merck Sinemet). Of calls discussing substitution in early 2011, patients and family members frequently sought advice on how to obtain insurance coverage for the more-expensive branded drug. It was commonly reported that patients did not feel the effects of the generic as quickly as with Merck Sinemet, and that the effects waned quicker. Several callers reported that the generic, even at maximum effect, was not as good as Sinemet. One patient reported that after generic substitution, she had to have her DBS settings adjusted to compensate for the decreased medication effect. Patients and caregivers reported worse sleep, worse dyskinesia, and an increase in impulsivity. None reported a preference for the generic version.

The challenges with taking a generic are compounded when patients receive differring generic formulations at each refill. In a report written by neurologist Criscely Go, MD, from the University of Florida together with NPF medical director Michael Okun, MD and several co-authors, Dr. Go suggests that the FDA's bioequivalency standard for generic drugs is not sufficiently rigorous to ensure equal efficacy in anti-parkinson medications. For example, the FDA's requirement is that a generic drug delivers between 80% and 125% of the medication delivered by the brand-name medication. This translates into the situation that two generics—

or two lots of the same generic—might differ by more than half the medication delivered.[1] The FDA has allowed the delivery of a different generic manufacturer's formulation for each refill request. Beyond this formulation issue, there may be other chemical differences in the generic that translate to differing efficacy.

While many patients do tolerate generic substitution, the authors recommended that generic substitution be treated as a medication change, and that it be managed by a patient's physician.

Further, the plan for effecting the medication change should be sensitive to a patient's particular need, and their past history with different forms of levodopa. Patients with a history of poor results when switching to a generic form despite dosage adjustments should be considered for brand drug.

The 2010-2011 Worldwide Sinemet Shortage

In early 2010, international news organizations and patient groups began to raise an alarm about Sinemet and generic carbidopa/levodopa both being unavailable.[2] The global supply shortage was officially confirmed in a letter from Michael Rosenblatt, MD, the Chief Medical Officer of Merck, dated August 19, 2010, sent to Amy Comstock Rick, the Chief Executive Officer of the Parkinson's Action Network (PAN), in response to a letter from Ms. Rick.[3] Because of the letter's wording, readers inferred from the letter that the acute shortage was, in fact, already resolved, except with respect to Sinemet CR in a small number of countries. The letter also stated that, "with respect to your question about the supply status of SINEMET in the United States, supply is currently available" and also that Sinemet was available in Canada. When referring to the supply shortage, Dr. Rosenblatt used the past tense, which suggested to many readers that the acute phase of the shortage was over.

Four months later, on December 20, 2010, Dr. Rosenblatt wrote another letter to Ms. Rick. This time, Dr. Rosenblatt announced that a temporary shortage of Sinemet would occur in the USA. Merck had applied to the FDA to change manufacturers of Sinemet from Merck to Mylan, and Merck took over the distribution of Sinemet from Bristol Myers Squibb. Merck reported that a temporary shortage might occur "across some of the dosages."

[1] If one generic delivers 80% of the medication delivered by the brand name and another 125%, the difference is 45% of the medication in the original. Comparing the two generics, the second generic delivers 56% more medicine than the first, or 45%/80%.

[2] See: "Parkinson's patients warned of medication shortages," CTV News Canada, January 28, 2010.

[3] The full letter is available on the PAN website.

NPF got its first call regarding the shortage of Sinemet shortly after launching its Helpline in August 2010. Two days before the first letter to Ms. Rick on August 17, 2010, a caller from Canada reported that Sinemet was not available. Starting January 7, 2011, NPF started receiving calls from Canada reporting that Sinemet was not available. Starting January 7, 2011, NPF started receiving regular calls regarding the shortage, with multiple calls on January 10 and regular calls continuing until April 22. Over that time period, callers to the Helpline wanted to discuss a variety of ways that the shortage was affecting them. Several callers inquired about the shortage, while simultaneously reporting on the inefficacy of the generic. Callers reported on misinformation from pharmacists who said that Sinemet had been discontinued.

Several pharmacies checked their national inventory system and stated they found no Sinemet listing.

The shortage was reported to the FDA. The FDA listed the Sinemet shortage on its "resolved shortages" web page and listed the resolution date as February 22, 2011.

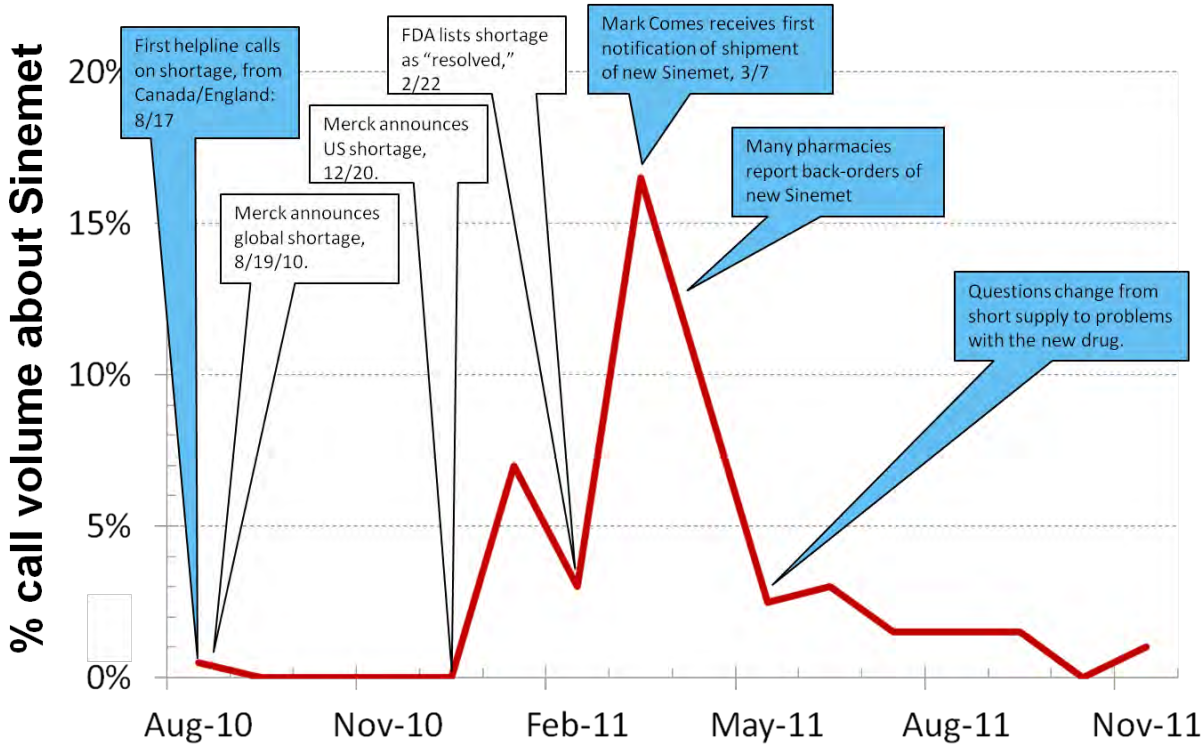

Figure 1: Volume of calls regarding the Sinemet shortage. Note that the first call came in before NPF began marketing the helpline in October 2010.

However, working with pharmacist Mark Combs, (who writes NPF's Ask the Pharmacist page on *Parkinson.org*) NPF received the first notification that the shortage was coming to an end on March 7. On that day Combs received word from his wholesaler that the immediate release Mylan Sinemet, was in stock and being produced in the 10/100 (NDC: 00006-3915-68) and 25/100 (NDC: 00006-3916-68) dosages. Immediate release Sinemet in 25/250 (NDC: 00006-3917-68) was not in stock.

Mylan Sinemet CR 25/100 and 50/200 (00006-3918-68 and 00006-3919-68) were not available, but had a possible release date in April. Combs's guidance for the Helpline was to steer people to the available doses, and to suggest that PD patients and families ask their pharmacists to search their networks or call their wholesaler for the drugs and check other chains if it were not available.

The next day, NPF received official notification of the approval of the new supplier. From the start of the shortage, NPF had been referring callers to Merck's information line. Despite the official notification of Sinemet availability, callers to the Helpline reported that when they called Merck, *they were given little information other than to have the pharmacist call their professional line.* Reports at that time were that the pharmacists were told simply that new medication was on its way. The NPF Helpline team reported that the common theme in calls was one of acute frustration, with replacement medications perceived as less efficacious than Merck Sinemet.[4]

For some time after the announced end of the shortage, demand for the new Sinemet outstripped supply. Combs reported in mid-March that Sinemet 25/100 CR, 50/200 CR, 10/100 IR, 25/250 IR, and 25/100 IR—essentially *every* Sinemet pill—was on back-order. Combs recommended that patients schedule an appointment with their neurologist to manage a medication transition. His guidance was that dosages generally change upon transition between formulations, and that it would likely take time to arrive at the proper balance. In addition, Combs felt that some patients who had trouble with the generic could be best served by transition to another branded medication such as Stalevo or Paracopa. However, such a medication transition would require the guidance of a physician.

Compounding the issue was the fact that many pharmacists were confused because there was a change in the National Drug Code, with little communication from the Company. Combs's guidance was that if a patient was told that Sinemet was discontinued, their pharmacist was using the old code. If they were told it was on back-order, they were using the correct code.

[4] Note that based on the research into placebo response performed by Jon Stoessl, MD, of the University of British Columbia and others, it is possible that either the generic drugs were biologically less efficacious than the branded drug or that patients confronted with unexpected and confusing challenges, presented at the pharmacy counter rather than managed by their neurologists, experienced a reverse placebo effect.

It was suggested that patients ask their pharmacist to check other pharmacies in their network and to try other pharmacies. Again, this was in March 2011, after the shortage was officially deemed resolved.

As the shortage continued to affect patients, people seeking their medications reported worsening of symptoms. As the new Sinemet was delivered to pharmacies, patients and their providers still reported that they were confused by the change in the National Drug Code.

Mylan Sinemet

The new Mylan Sinemet, once available, has been reported to be different from the prior formulation. These differences have been reported not only clinically but also in the pills physical characteristics. Old Sinemet was scored for easy splitting, and many patients commonly split their pills to manage their dosing. **The new pills were not scored and patients reported the pills crumbling** unless split with a razor blade—a clear safety issue for a person with Parkinson's. Beyond this, the new pills seemed to dissolve easily. Callers to the NPF Helpline characterized this as "melting" if held in the hand, or even in clothing next to the body.

Patient-reported perception of the efficacy of the Mylan Sinemet has been uniformly negative. Reports of the medication wearing off an hour sooner than previously were common and independently reported. Other reports were that the medication effects took longer to be felt than previously. Multiple patients reported that Mylan Sinemet at its maximum effect was less than Merck Sinemet despite attempts to optimally titrate it. The NPF Helpline received no positive reports.

Assessment

People affected by the Sinemet shortage uniformly reported a negative experience. The results of this negative experience included poor symptom management and dissatisfied patients and caregivers. Given this scenario, it would be difficult to describe the transition as smooth or with minimal impact. While NPF's helpline received several hundred total calls based on information from large pharmacy chains collected in this process, clearly the impact was much broader. Several aspects of the transition from Merck-manufactured Sinemet to Mylan-manufactured Sinemet at the beginning of 2011 provide important lessons. Should a similar transition be necessary in the future, the key points learned from this transition were:

Provide much clearer information much sooner and more broadly. In August of 2010, the unclear wording of the communication led the PD community to mistakenly infer that there would be no interruption in the supply of branded Sinemet, despite the experience in other countries. The first notification of the possibility of an interruption was sent on December 20, 2010, with the first reports of patients being affected starting less than 20 days later. This is too short of notice for people with parkinson's to amass the extra pills needed. This communication to the PD community referenced an ongoing process with the FDA, suggesting that the community could have been notified earlier. Further, with the year-end holidays just days away, the information about the interruption was likely missed by many patients and many neurologists were unavailable to help titrate a medication change. Had the community been notified earlier, patients could have had time to schedule appointments with their neurologists to discuss options.

At least three months advance public notice should be required so that patients will have an opportunity to discuss a medication change at a routine office visit, six months is better. Further, relying on one patient advocacy channel was simply not enough, given the importance of the issue.

Work with neurologists, physicians, and pharmacists to ensure that those who need the medication most get highest priority. Many patients will potentially tolerate generic substitution. With better information provided earlier, neurologists can work with patients on managing demand to help reduce the impact of the shortage on patients who may least tolerate change—which in Parkinson's, is likely to be those more advanced, and hence, more vulnerable. In addition, we would also recommend working with CMS, other insurers and pharmacy benefit organizations to help smooth the way for brand substitutions when a patient had difficulty with generic.

Work with natural partners to ensure that good information is available. NPF independently sought the details of the shortage, such as the change in NDC codes, and distribution information. Organizations like NPF and other patient and professional-focused groups have a mission to ensure that the right information makes it into the right hands in order to deliver the best care. If these organizations were informed earlier in the process about changes that might limit access—like the change in NDC code that resulted in patients being informed that their medication was no longer available—they would be willing partners in disseminating the information. This would have benefits to patients and also good-will benefits to the pharmaceuticals company or service provider.

New formulations need to take into account real-world patient needs. The ability to score medications for Parkinson's patients is a critical patient-care requirement that was not met in the Mylan formulation. The *formal clinical instructions* for the administration of levodopa include the use of half tablets.[5] In addition, the "crumbling" and "melting" aspect of the new formulation is highly important to people who must carry around multiple pills during the day. Any patient-centric effort must take such matters into account.

We believe that good patient service is good business. Bristol Myers Squibb, Merck, and Mylan all have achieved success by providing products that provide much relief to many people. As such, with any other condition, thoughtful, compassionate service is a best practice in Parkinson's disease.

The discovery of levodopa yielded a Nobel prize and the launch of Sinemet revolutionized Parkinson's care, to the point that carbidopa/levodopa is so much a staple of PD care that we can't imagine a world without it. In the first half of 2011, because of uncertainty and confusion some people were faced with a loss of this drug. It didn't have to be and, with all the stakeholders working more closely together with good information, we sincerely hope this way we could avoid this in the future.

[5] See, for example: Ahlskog, JE, Parkinson's Disease Treatment Guide for Physicians. Oxford University Press, 2009, pg 121; National Parkinson Foundation Parkinson's Toolkit, http://Toolkit.Parkinson.org/content/levodopa, 2011.

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1501 NW 9th Avenue
Bob Hope Road
Miami, Florida 33136

Parkinson.org web
305.243.6666 office
305.243.6073 fax
800.4PD.INFO helpline