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### How to Administer Fixed-Ratio Combinations of GLP-1 Receptor Agonists & Basal Insulin

Announcer: Welcome to CME on ReachMD. This segment, *How to Administer Fixed-Ratio Combinations of GLP-1 Receptor Agonists and Basal Insulin*, is provided by Global Education Group. Paradigm Medical Communications, LLC is the educational partner. The activity is supported by an educational grant from Novo Nordisk, Inc. Joining host Dr. Matt Birnholz are guest experts Dr. Wendy S. Lane, an endocrinologist at the Mountain Diabetes and Endocrine Center in Asheville, North Carolina, and Dr. Javier Morales, of Hofstra Northwell School of Medicine in Hempstead, New York.

Dr. Birnholz: Type 2 diabetes is a chronic, progressive disease affecting over 400 million people worldwide, which places huge burdens on individual patients and society, and it can be very difficult to treat due to both patient and clinician-related barriers. The fixed-ratio combinations of GLP-1 receptor agonists and basal insulin are the newest treatment options for managing type 2 diabetes, which may help overcome some of those barriers. Our discussion today will focus on fixed-ratio combinations and their applications in clinical practice. Drs. Lane and Morales, welcome to the program.

Dr. Lane: Thank you.

Dr. Morales: Thank you.

Dr. Birnholz: Let's have a look at the basics of how to use the fixed-ratio combination.

Video Segment 1 (runtime 2:06): Dr. Morales describes storage and disposal procedures for fixed-ratio combination pens containing a GLP-1 receptor agonist and basal insulin.

Dr. Birnholz: Dr. Morales, let me start with you. In your primary care practice, what are the biggest barriers to starting injectable therapy for your patients?

Dr. Morales: There are so many different factors that need to be taken into consideration. There are certain concerns on the patient's side: for instance, microvascular complications that may evolve from injection therapy. This is particularly common in people who have had a family member who may have been on insulin and who, because of the progressive nature of their diabetes, may have been undertreated, or may have developed either retinopathy or vascular complications. Even if you were to be using a GLP-1 receptor agonist as a noninsulin therapy, it is still perceived as an injection and oftentimes patients with these family histories will be a little bit apprehensive. On the physician's side, one of the big challenges that we have is the time factor and understanding how to use these agents, how to initiate breaking that injection barrier, and perhaps give a little bit of guidance during the course of therapy. Now, we do, in common, share the same concerns about hypoglycemia, and once a patient has experienced a major hypoglycemic event, I can't tell you how big a barrier that is to overcome when it comes to intensification in the future. Oftentimes, patients may negotiate or reduce their dosing of medications or maybe defensively overeat in order to circumvent hypoglycemia. That fear of hypoglycemia, in my opinion, is probably one of the biggest obstacles that we encounter when it comes to injection therapy, whether it be insulin or non-insulin therapies.

Dr. Birnholz: Thank you Dr. Morales, that's excellent. Dr. Lane, from the vantage point of your endocrinology practice, I'm sure there are some overlapping issues that you see compared to what Dr. Morales said but not necessarily completely overlapping. Is that correct?

Dr. Lane: Yes, that's true. Definitely, the biggest fear—I completely agree with Dr. Morales—is that of hypoglycemia, and it should be. It is potentially a devastating complication of insulin therapy. It can have terrible consequences, and once the patient experiences significant hypoglycemia, you will have a very hard time convincing that patient to intensify insulin therapy or to increase their insulin dose. So, that probably is our biggest barrier as endocrinologists—the limitation of the therapy itself. It can be difficult and dangerous therapy if not done properly or in a patient who isn't monitoring their glucose regularly. Probably the second biggest concern that our patients bring up to us is weight gain associated with therapy, and of course, that reflects mostly insulin therapy. The noninsulin agent we use as insulin-sparing agents, especially the GLP-1 receptor agonist class, which mitigates associated weight gain, is very useful to us because patients are very concerned, and fear weight gain. Once in a while, a patient with hand problems such as arthritis or diabetic arthropathy, where their hand is stiff, may have trouble operating the device, pushing the plunger on the injection device, or drawing up from the syringe. Occasionally, vision may present a problem. They may need assistance.

Dr. Morales: To further touch upon physical challenges that patients may experience, we have an older population now. You talked about diabetic arthropathy, and it's probably a lot more common than we realize, but what's kind of nice about these devices is that for those patients who may have these challenges in terms of thumb dexterity, at least one of the devices doesn't have an extendable plunger; it's just a dial and a push-button. Then, there also are the audible clicks for those who may be visually challenged. I know I personally had a couple of patients who were legally blind whom I started on injection therapy, and it's very nice that the device does offer a click for every unit to be delivered. It makes life a little bit easier.

Dr. Birnholz: With those points in mind, let's take a look at how to inject these fixed-ratio combinations of basal insulin and GLP-1 RAs.

Video Segment 2 (runtime 5:37): Dr. Morales instructs a patient in how to dial a dose and administer an injection with each fixed-ratio combination pen.

Dr. Birnholz: Dr. Morales, you had talked about some of the barriers from your standpoint as a primary care physician, including the fear of injections. Dr. Lane, does that same fear exist for you in your practice?

Dr. Lane: Very rarely, somebody will be afraid of an injection. We can almost always overcome this by actually showing them the injection device and the needle that goes on the injection device. We have them take their first injection right in the office, and that technique seems to have overcome a lot of the injection barrier. When people see how small the needle is and they feel that there is minimal, if any, discomfort associated with the injection, they're fine after that. It's more anticipatory that they are thinking, "Oh, this is going to be some huge, painful device," and it really is not.

Dr. Morales: There was a nice publication in 2007 in the *Journal of Diabetes Complications* by Nakar (Nakar S, et al. J Diabetes Complications. 2007;21:220-226.). They looked at family physicians and insulin-naïve patients, and they cued in on concerns over weight gain, hypoglycemia, injection pain, and pain from blood tests. It wound up that about 90% of the family physicians who were queried actually expressed significant fear of hypoglycemia, pain from injection, and pain from blood tests, whereas about 20% of the patients reported these concerns. So certainly, I think there is a lot of apprehension; it's more so from us, the prescribers, the practitioners, than it is on the part of the patient.

Dr. Birnholz: Dr. Morales, that sounds like it feeds into that concept of what is loosely called insulin inertia, that reluctance to prescribe insulin. Is that correct?

Dr. Morales: It is. I think it's applicable for all injectable therapies.

Dr. Birnholz: I want to shift over to the question of how patients are selected, and specifically, become the right candidates for these fixed-ratio combination agents that we've been talking about. Are there any restrictions on who should receive them? Dr. Lane, let me start with you.

Dr. Lane: All the GLP-1 receptor agonists are contraindicated in patients with a personal or family history of medullary carcinoma of the thyroid, which is not the most common thyroid cancer. It's actually very uncommon, but it is a contraindication because of rodent data that showed that there was a slight increase in the rate of this cancer in rodents treated with GLP-1 receptor agonists. Patients who have this personal or family history, or if they have it as part of a larger syndrome called MEN (multiple endocrine neoplasia 2), should not use it. Of course, if a patient did take a prior GLP-1 receptor agonist and had a very, very bad reaction, usually gastrointestinal reaction such as nausea and vomiting on the lowest dosage of that previous GLP-1, you may want to proceed with caution, but I wouldn't rule out trying these combination agents even if the patient had mild GI side effects from a previous GLP-1, because they will be using, in all likelihood, a lower dosage when they use it in combination with insulin, and they very well may tolerate that.

Dr. Birnholz: Dr. Morales, who would be the ideal candidate for you?

Dr. Morales: When it comes to the pancreatitis, the warning does say that you need to be a little bit careful about pancreatitis when it

comes to the appropriate selection of therapies in patients with diabetes. I guess the GI intolerance is kind of interesting as well. There seems to be a dosage-related effect with respect to GI intolerance, but fortunately what's nice about these combination products is the fact that it's nicely tolerated by virtually all patients because the GLP-1 levels never really get to the high pharmacologic dosages that we ordinarily would use in solo pharmacotherapy. I think that these combination products have a lot to recommend them with respect to the tolerability of the agent, the risk of the weight gain with intensification of therapy like Dr. Lane had mentioned. Also, the risks of hypoglycemia seem to be somewhat lower.

Dr. Birnholz: What about the problem of adherence to injectable treatments? I know that both of you use strategies to help overcome this particular barrier, but Dr. Morales, just staying with you, what's your perspective on helping to improve patient adherence to these injectable treatments?

Dr. Morales: I think, first and foremost, that the channels of communication need to be maintained open, so being accessible to your patients, answering whatever questions that they may have during the course of their titration phases is very, very important. More frequent follow-up visits after initiation of therapy will ensure that at least lifestyle modification is being implemented, but more importantly, it allows you to query how tolerable the agent is or has been. So, communication is always the key, being accessible whenever you can.

Dr. Birnholz: Dr. Lane, any additional thoughts on adherence?

Dr. Lane: Really, I agree with everything Dr. Morales pointed out. One of the big benefits of these combination agents is that you're getting two injections in one. You probably, in a large population using them, won't need to intensify to mealtime insulin, and so your chance of adherence just with one injection per day goes up, and I think that's just the nature of this product. It's going to improve adherence right off the bat, but in terms of other tricks that would improve adherence, I totally agree; I think a well-educated patient is always your best ally. When these patients understand the mechanism of how these drugs work and how the GLP-1 component is going to prevent most of the weight gain associated with insulin and reduce the chance of hypoglycemia associated with insulin, and when they see the effect on their blood sugar and their weight, I think they are going to be very pleased with the results and see their success early on. That itself is going to create a cycle of adherence where they see good things happening, so they keep taking the medication.

Dr. Birnholz: Well, with those great parting thoughts, I want to thank Dr. Lane and Dr. Morales for sharing their clinical expertise with us today. Doctors, it was great having you both on the program.

Dr. Lane: Thank you for having us.

Dr. Morales: Thanks very much for inviting us.

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