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### A New Innovation in the Prevention of Birth Prior to 37 Weeks Gestation

Announcer:

This is CME on ReachMD. This activity, Advances in Preterm Birth Prevention, Subcutaneous versus Intramuscular Dosing of 17 Alpha-hydroxyprogesterone Caproate: Pharmacokinetic Profile, Patient and Practitioner Impact, is provided in partnership with Omnia Education and supported by an independent educational grant from AMAG Pharmaceuticals, Inc.

Before beginning this activity, please be sure to review the learning objectives and faculty disclosures.

Your host is Dr. Amy Mackey.

Dr. Mackey:

The Society for Maternal-Fetal Medicine, SMFM, the American College of Obstetrics and Gynecologists, ACOG, and the American College of Nurse-Midwives, ACNM, have all published guidelines providing specific recommendations regarding the diagnosis and management of patients at risk for preterm birth. In light of the availability of a subcutaneously administered 17-hydroxyprogesterone caproate, this ReachMD panel discussion will seek to provide OB/GYN clinicians with information surrounding the pharmacokinetic principles underlying the determination of pharmacologic bioavailability and bioequivalence and the clinical data supporting the bioequivalence of 17-hydroxyprogesterone caproate administered subcutaneously compared to the intramuscular injection. It will also define the impact of this new route of 17-hydroxyprogesterone caproate administration on patient and practitioner parameters.

Welcome to CME on ReachMD. I'm Dr. Amy Mackey and joining me to review these strategies are Drs. Baha Sibai and Judith Smith from the University of Texas Health Science Center. Dr. Sibai is a Professor in the Department of Obstetrics, Gynecology and Reproductive Sciences, and Dr. Smith is an Associate Professor and Clinical Pharmacy Specialist in the same department.

Dr. Baha Sibai and Dr. Judith Smith, welcome to the program.

Dr. Sibai:

Thank you for having me participate in this exciting scientific activity.

Dr. Smith:

Thank you so much for having me.

I'm glad to be here today. I look forward to the discussion.

Dr. Mackey:

Dr. Sibai, as I noted in my opening remarks, the Society for Maternal Fetal Medicine, the American College of Obstetrics and Gynecology and the American College of Nurse-Midwives have all developed guidelines that provide specific recommendations for the diagnosis and treatment of preterm birth. Can you give us an overview of these organizations' recommendations?

Dr. Sibai:

ACOG, SMFM and ACNM have published clinical guidelines starting in 2012 and ending in 2017, and these guidelines have

emphasized the use of progesterone in the management of patients at risk for spontaneous preterm birth. These recommendations suggested that for women who have a history of previous spontaneous preterm birth at less than 37 weeks, that women should receive 17-hydroxyprogesterone caproate for the prevention of recurrent preterm birth. This recommendation includes starting the medications at 16 weeks and continuing until 37 weeks gestation. For women without a history of spontaneous preterm birth who had a routine cervical ultrasound, a cervical length of less or equal to 20 mm, they recommended that these women should receive vaginal progesterone starting at 18 all the way up to 24 weeks gestation. In addition, they emphasize that women who have multiple gestation should not receive 17-hydroxyprogesterone or vaginal progesterone to prevent preterm birth.

Dr. Mackey:

Dr. Smith, again, as I noted in the introduction to this program, the availability of a new route of administration of 17-OHPC FDA-approved from intramuscular to subcutaneous may raise questions as to what this means pharmacologically to the patient. From what I understand, the subcutaneous route of administration had to demonstrate comparable bioavailability and bioequivalence to the IM route of administration. Can you spend a few minutes explaining what these terms mean and what needs to be done to demonstrate this?

Dr. Smith:

Very good question. So, bioequivalence by definition is when a study needs to demonstrate the absence of a significant difference between both the rate and the extent of which drug becomes available at the site of action when administered at the same concentration or same dose in an appropriate designed study. Now, bioavailability has a similar definition. It's the degree at which the rate of the drug is absorbed and available at the physiological site of action, and this is often described as the total exposure or area under the curve, AUC, which may sound a little bit more familiar to the clinicians in the audience. The very simplified pharmacokinetic equation for bioavailability or area under the curve is dose over clearance, and this is why bioequivalence studies need to typically be done at the same dose of the active medication. For a manufacturer to actually claim bioequivalence, the study must demonstrate that there is no significant difference between the rate or time to the maximum concentration, or Cmax, and the extent or area under the curve between either the new formulation or new route of administration of a drug. The FDA guidance allows the product to have anywhere between an 80% to 125% variability from the original product or route to claim bioequivalence. The one caveat that we often miss in this is that this also has to have a 90% confidence interval when all the values within that confidence interval range also have to be within that 80 to 125% variability of the original product. So there are some stringent guidelines to claim true bioequivalence.

Dr. Mackey:

As our learners know, 17-OHPC is already available, but the current formulation is administered IM. Dr. Smith, how does this new subcutaneous formulation compare with the IM formulation in terms of bioavailability based on the published clinical data?

Dr. Smith:

There is one study by Krop and colleagues that has looked and compared the IM versus the sub-cu route of administration. This was a multicenter study in postmenopausal women after a single dose of the 17-hydroxyprogesterone. There were 90 patients included in the study, 45 patients on each arm. They compared the 250 mg IM dose to the 275 mg subcutaneous dose. If you look at this table on the slide, you can look and compare the pharmacokinetic parameters for the 2 routes of administration, and focusing on the bioequivalence, the key components were the rate and the total exposure or extent of exposure. So looking at the Cmax and Tmax, you can see between the 2 arms that they are similar for both the subcutaneous and the IM administration, and the total exposure, which is described as AUC, in all the time intervals evaluated were similar between the 2 routes of administration. There was a slight difference in the half-life for the subcutaneous route, was slightly longer compared to the IM, but overall, these 2 routes of formulations were deemed bioequivalent based on being within that 80 to 125% interval for claiming bioequivalence.

The other aspect to look at a new route of administration is the tolerability. On this next slide, we can compare the reported adverse events from both the patient perspective as well as what was observed by the study investigators, and the only thing I'd like to highlight is the differences at the injection site pain where we can see that the subcutaneous route reported a higher incidence of pain at the site of injection compared to the IM route.

When we look at this study, the only major limitations is the study population as well as the study design of a single dose versus multidose, and looking at the bioequivalency, what factors influence bioavailability in the patient population. Postmenopausal women versus pregnancy have some variable differences in pharmacokinetics, primarily looking at differences in plasma protein binding, looking at differences in the volume of distribution as well as metabolism.

Dr. Mackey:

Dr. Smith, you noted that the most common side effect with the subcutaneous injection was injection site pain with nearly 40% of patients receiving the subcutaneous injections reporting this versus nearly 10% of patients receiving the IM injections. Of the

subcutaneous patients, 85% reported this as only mild pain. Any explanation as to why this difference existed, particularly given the smaller size of the subcutaneous needle versus the IM needle, which is 27 gauge versus 21 gauge respectively?

Dr. Smith:

So I don't think the pain of injection is anything to do with the needle but actually the drug itself. The 17-hydroxyprogesterone is formulated in a combination of both 40% alcohol as well as castor oil, and these diluents can be an irritant to the tissue.

Dr. Sibai:

May I comment on that? Okay, as I read this question, interesting this morning I was seeing the patients in my office. I asked all of our nursing staff and the nurse manager about did they have any complaints from the patients about the sub-cu injection. I was really surprised they said they didn't have a single patient among the 22 women who received this medication starting April in my office.

Dr. Mackey:

If you are just tuning in, you are listening to CME on ReachMD. I am your host, Dr. Amy Mackey, and I have the pleasure of speaking with Dr. Baha Sibai and Dr. Judith Smith on the topic of preterm birth.

Dr. Sibai, considering the availability of the subcutaneous auto-injector, how has this affected your clinical management of your patients eligible to receive 17-OHPC?

Dr. Sibai:

I think that there are really 2 important issues in this case: first, the compliance by the patient, and more important, the satisfaction by the nursing and the staff in my office, so that's the first issue. In the past year, before I started prescribing the subcutaneous injection, my experience has been about 10 to 15% of all women who are eligible to receive Makena, they were refusing to take anything, and their reason for that was that they didn't like to take IM injections and they didn't want to come every week to have somebody give them the injection in the office. The other thing, few of them said that either they had a friend or a sister who told them that she received the medicine and it is so painful and this is why they elected not to take it. Then I will say an additional probably 15% of the women where we started giving the IM injection—about 15% of them were not really compliant by taking the doses every week, and this really was a major concern.

What I can state now is that once I started using this in April, the compliance was tremendous. I haven't had a single... I know it was only a short time period, about 3, 4 months. I haven't had a single patient who really refused to take the injection if she is eligible to have it. And second important thing, I asked the question about what percentage of our patients actually have now shifted from the IM to the subcutaneous, and the answer is probably now about more than 75% of my patients now are opting to receive the subcutaneous injection. And the main reason most likely is because the needle size is very small, the auto-injection is very easy to teach the patient how to take it.

Dr. Mackey:

And what has been the reaction of your staff to this?

Dr. Sibai:

I tell you the staff really loved it because, first, they don't have to worry about, you know, the patients have to come every week to the office, the time they spend, you know, to give the injection to the patient, plus for safety issue, the way the needle and injection. Now it is very safe, even when the patient receives it in the office, for our staff nurse to give the injection, so really it has safety issue. Again, for me, I think it's one of the most important things I see now for compliance with the medication. Again, we are fortunate here that Medicaid and the commercial insurance have approved it. I haven't had anybody really being denied, which is really a very big plus now for using it.

Dr. Mackey:

From your response, would it be accurate to say that the availability of the auto-injector will likely enhance patient adherence to this therapeutic regimen?

Dr. Sibai:

Absolutely, there is really no doubt. I really think hopefully we'll be able to show that it has the same efficacy and probably the outcome will be better because you have better compliance.

Dr. Mackey:

I want to thank you both for a very informative program on the most important issue surrounding obstetrics: the prevention of preterm birth. The information you provided will allow our listeners to understand the role of new routes of administration of 17-OHPC via subcutaneous administration in the upper arm in their patients at risk for preterm birth owing to prior spontaneous preterm birth. Is there

anything you would like to say in closing?

Dr. Sibai:

Absolutely. Really, I need to assure the providers, because again, I have some phone call about, you know, is this really medication any different than Makena? And there really are providers I have to really assure that it's the same medication. It's just being put in a different syringe and being given a different mode.

Dr. Mackey:

Well, this has been a very insightful discussion on one of the most important issues surrounding obstetrics, which is the prevention of preterm birth. Dr. Sibai, Dr. Smith, thank you for joining me.

Dr. Sibai:

Thank you for having me today.

Dr. Smith:

Thank you so much for having me.

Announcer:

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