Makena or Compounded 17P?

To the Editor:

I read with great interest the article in the July issue of *P&T*, entitled "Controversies in Practice," by Drs. Patel and Rumore regarding weekly injections of 17P for the prevention of preterm birth.[1] Lacking, sadly, was a return on investment (ROI) comparison as well as a summary of the facts surrounding this controversy. Had those been included, I am confident that the authors would have arrived at a very different conclusion. Absent that, they came up with a costly recommendation that accrues no proven additional health care benefit.

Pharmacoeconomic Comparison

Assume that 200 patients experienced a previous preterm birth. All of these women received hydroxyprogesterone caproate (Makena), self-administered compounded 17P, or nurse-administered compounded 17P in the home. The advantage of nurse-administered injections is that compliance can be monitored; this alleviates a problem identified in a trial conducted by the National Institutes of Health.[2] One could reasonably expect 40%, or 80 patients, to deliver a preterm infant if none of the 200 were treated. If all were treated, about 33% of those who would have delivered early (26 patients) would be spared. The average cost of a preterm birth is roughly $49,000, compared with $4,500 for a healthy birth, according to the March of Dimes.[3] Therefore, all three treatment methods could be expected to yield savings of $49,000 x 26 patients = $1,274,000.

The ROI can be easily calculated by multiplying the total cost of the intervention and dividing by the savings. An example of each method follows:

1. Self-administered compounded 17P costs $15 per injection x 20 weeks = $300 per pregnancy x 200 treated patients = $6,000 total cost; $1,274,000 divided by $600 = $212 ROI. Therefore, for every $1.00 spent, $212 is saved.
2. Compounded 17P injection, administered by a home nurse, costs approximately $150 x 20 weeks = $3,000 per pregnancy x 200 patients = $600,000 total cost; $1,274,000 divided by $600,000 nets a respectable $2.12 ROI; simply put, for every $1.00 spent, approximately $2.12 is saved.
3. Makena costs approximately $15,000 per pregnancy x 200 treated patients = $3,000,000 total cost. Divide the total cost by the savings, and the ROI comes out to *negative* $2.35. As a result of the high cost of Makena, $2.35 is spent to save $1.00! For Makena to cost as much as it saves, the price per pregnancy would need to be reduced from $15,000 to $6,370 ($1,274,000 savings divided by 200 patients).

Fact Summary

- Compounded 17P was in use exclusively from 2003 until Makena was approved on February 4, 2011, with no evidence of harm resulting from the compounded drug.
- The FDA supports the use of compounded 17P.
- The American College of Obstetricians and Gynecologists (ACOG) is supportive of compounded 17P use for the appropriate clinical indication.
- The Society for Maternal-Fetal Medicine has not found any problems with compounded 17P use. George Saade, the society's President, said:[4]

> The Society for Maternal-Fetal Medicine commends the FDA on its recently released position that it will exercise enforcement discretion with respect to compounding hydroxyprogesterone caproate. This action will ensure that this lifesaving treatment will continue to be available for all those who need it. Affordable access to hydroxyprogesterone caproate is critical in ensuring the health and full-term birth of babies in the U.S.

- No randomized controlled trial has ever demonstrated improved birth outcomes or a more favorable safety profile of Makena compared with compounded 17P.
- Compounded 17P is substantially equivalent and readily available anywhere in the U.S.

When a pharmacoeconomic comparison is performed and the facts are assembled, it is difficult to imagine how the authors could conclude that Makena should be used. The only explanation is the overemphasized and unfounded concern regarding liability. In reality, one has to wonder how this qualifies as a controversy when the issue seems so clear.

References

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Sincerely,

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Note: American HomePatient provides services to patients with respiratory illnesses and is not involved in women's health. Mr. Reichmann has no financial or commercial conflicts of interest in regard to this letter. He has published articles on women's health in *Obstetrics & Gynecology, Managed Care, the Journal of Reproductive Medicine,* the *American Journal of Obstetrics and Gynecology*, and *Nature*.

See next page for the authors' response.

The Authors Reply:

Thank you for the opportunity to respond to Mr. Reichmann's letter in which he conducts a return on investment (ROI) and opines, "When a pharmacoeconomic comparison is performed and the facts are assembled, it is difficult to imagine how the authors could conclude that Makena should be used. The only explanation is the overemphasized and unfounded concern regarding liability."

The purpose of our article was to explain the twofold controversy created by the FDA and KV Pharmaceutical Company (KV). First is the unique situation that was created when the FDA approved hydroxyprogesterone as an orphan drug while simultaneously allowing compounding pharmacies to compound the commercially available product. Inadvertently, the first controversy leads to the second—which is whether individual organizations should add Makena to their formularies, given that the addition or rejection is based not on the presence of an alternative therapy with a different drug but on the presence of the same drug as an alternative at a dramatically lower price.

Mr. Reichmann's ROI analysis is flawed, in that it does not consider patient-assistance programs, vouchers, and company rebates. For example, uninsured patients with annual gross household incomes of less than $60,000 pay nothing for the drug under an assistance program. In any case, a ROI analysis is unnecessary, since one can readily identify the more cost-effective option without any calculation. In addition, although cost containment is an important factor in determining whether one drug should be used over another, other factors merit consideration. The original controversy may seem to be the drug cost. However, beyond the cost issue lie questions for which we do not have answers.

Mr. Reichmann's view is based on a six-point fact summary, of which we take issue with at least four points:

1. *The American College of Obstetricians and Gynecologists (ACOG) is supportive of compounded 17P use for the appropriate clinical indication.* The following ACOG statement fails to imply support:[1]

> Significant quality concerns may exist for compounded agents, particularly when sterility is important (e.g., injectable and inhalation agents). … [P]hysicians and patients should exercise caution in prescribing and using products that are largely untested for safety and efficacy.

2. *The FDA supports the use of compounded 17P.* After publication of our article, the FDA released a Questions and Answers document to clarify its June 15 statement,[2] asserting:

> If there is an FDA-approved drug that is medically appropriate for a patient, the FDA-approved product should be prescribed and used. Makena was approved based on an affirmative showing of safety and efficacy. … Therefore, when an FDA-approved drug is commercially available, the FDA recommends that practitioners prescribe the FDA-approved drug rather than a compounded drug unless the prescribing practitioner has determined that a compounded product is necessary for the particular patient and would provide a significant difference for the patient as compared to the FDA-approved commercially available product.

Again, this statement hardly suggests support.

Despite the FDA's statement, on July 5, 2012, KV filed a lawsuit against the FDA for allegedly abrogating Makena's statutory 7-year orphan drug market exclusivity in violation of the Orphan Drug Act of 1983 by giving *de facto* approval to compounded versions of 17P intended for use for the same indication for which Makena was approved.[3] Exclusivity under the Orphan Drug Act can be curtailed in only three circumstances: (a) when sufficient quantities are unavailable (i.e., access), (b) when the FDA revokes orphan status, and (c) when the exclusivity holder consents.[4]

KV appears to be in financial trouble; it recently filed for bankruptcy.[5] Even if the company prevails, an Abbreviated New Drug Application (ANDA) has already been filed for generic injectable 17P, which would allow for off-label use for the same indication as Makena.

3. *Compounded 17P is substantially equivalent and readily available anywhere in the U.S.* Several states recognize that compounded 17P might not be available. The Kentucky Department of Medicaid Services allows for Makena approval if there is "no access to a pharmacy which can compound 17P."[6]

4. *The Society for Maternal-Fetal Medicine has not found any problems with compounded 17P use.* This flies in the face of recent acknowledgments by this group that there are inherent differences between FDA-approved Makena and compounded 17P formulations and that compounded formulations are made under less stringent conditions with a greater potential for human error.[7]

Turning to the commentary regarding overemphasis on liability, we note that compounding pharmacy indemnification clauses will not save the day. Medical malpractice insurance is not likely to cover compounded drugs when there is an FDA-approved product in its place. In a survey (albeit a KV-sponsored one) of 401 obstetricians, 39% felt that professional liability was somewhat or very important in their decision not to prescribe compounded 17P, and 46% agreed with the statement that there is more professional liability when prescribing compounded 17P when an FDA-approved product is available.[8]

The liability of hospital pharmacies and physicians using a compounded medication *when an FDA-approved version is available* might not be fully appreciated by all readers. The American Society of Health-System Pharmacists guidelines[9] state:

> The pharmacy director must take complete responsibility for patient outcomes from all medication-related activities performed at or for the organization's work sites, whether they are carried out by the organization or [by] contractors' staff on or off site.

If patients are unaware that their physicians are using non-commercial products *when commercial products are available*, legal recourse could be significant, especially if ill effects or death from a contaminated or erroneously concentrated product occur. Therefore, all risks should be explained, and informed consent should be obtained from the patient who is

using a compounded 17P product. Incidentally, were it not for this unique situation in which an FDA-approved product exists, the authors of the *P&T* article (both of whom are pharmacists) would also advocate for the compounding of 17P.

Events that have occurred, including a lawsuit against the FDA, indicate that we can't afford to take a simplistic view of the current situation. A larger controversy—beyond the question of whether to add the drug to a hospital formulary—now exists, namely that of balancing the costs and accessibility of Makena against the strong public interest in preserving the incentives for development of orphan drugs. Perhaps the time has come for amendments to the Orphan Drug Act, as pricing exploitation under this act has become routine.

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Sincerely,

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Clarification on Hydrocodone (Zohydro)

To the Editor:

I am reaching out on behalf of Zogenix and wanted to provide additional information and clarification in response to the recent P&T editorial (July 2012, page 399), titled "Hydrocodone Rescheduling Amendment and Pipeline Products on the Horizon" and its characterization of Zohydro, as the statement as published is incorrect.

While the piece correctly discusses the fact that Zogenix submitted a New Drug Application (NDA) to the FDA in May 2012 for Zohydro™ (hydrocodone bitartrate extended-release capsules), the piece also makes a mistaken reference to the amount of hydrocodone found in Zohydro as compared to Vicodin, and we felt it was important to clarify this point.

Zohydro uses the active ingredient hydrocodone, which is the same active ingredient found in hydrocodone combination products such as hydrocodone/acetaminophen (Vicodin) or hydrocodone/ibuprofen. Zohydro is an extended-release formulation, which means the medicine is released over a longer period of time, 12 hours, versus the immediate-release products that are currently available. Those products are dosed more frequently at 4 to 6 hours. Zohydro will be available in a variety of dosage strengths that will allow physicians to customize dosages to the individual needs of patients with chronic pain.

In addition, we wanted to add that Zogenix submitted a comprehensive Risk Evaluation and Mitigation Strategy (REMS) program in the Zohydro NDA with the intent of reducing inappropriate prescribing and the misuse of the product while maintaining access to patients suffering from chronic moderate to severe pain. If approved, Zohydro will also be regulated as a DEA Schedule II product, which will have stricter prescribing and refill limits than Schedule III products.

Sincerely,

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