DEPARTMENT OF HEALTH AND HUMAN SERVICES
OFFICE OF DIRECTOR

ACTION REFERRAL

TO	DATE
Singleton	2-21-12

DIRECTOR'S USE ONLY	ACTION REQUESTED
1. LOG NUMBER 10319	[X] Prepare reply for the Director's signature DATE DUE 2-28-12
2. DATE SIGNED BY DIRECTOR cc: Mr. Keck, Giese, Kost Extend until 3/7/12, see attached e-mail.	[ ] Prepare reply for appropriate signature DATE DUE [ ] FOIA DATE DUE [ ] Necessary Action

APPROVALS (Only when prepared for director's signature)	APPROVE	* DISAPPROVE (Note reason for disapproval and return to preparer.)	COMMENT
1. Cleared 3/22/12, letter attached.			
2.			
3.			
4.			

Via Federal Express

Leg. Smith
C: Director
BE.
D. Sign -

February 20, 2012

Anthony E. Keck
Director
State of South Carolina
Department of Health and Human Services
1801 Main Street
Columbia, SC 29202-8206

Re: Makena®

Dear Director Keck:

As President and Chief Executive Officer of K-V Pharmaceutical Company, the parent company of Ther-Rx Corporation ("Ther-Rx" or "Company"), I write to request a meeting to discuss the current coverage policy of the South Carolina Department of Health and Human Services (the "Department"") for Makena®. For the reasons set forth below, the Company believes that the current policy is in violation of Federal Medicaid law and Ther-Rx's Medicaid Drug Rebate Agreement ("Rebate Agreement") with the Centers for Medicare & Medicaid Services ("CMS"). Of particular concern, SCDHHS's policy effectively denies underprivileged pregnant women in South Carolina at risk for preterm birth access to the only FDA-approved drug for their medical condition, while FDA-approved Makena® is readily available to mothers who have commercial insurance.

Makena® is a sterile injectable drug, whose active pharmaceutical ingredient is hydroxyprogesterone caproate or "17P." It is the only drug specifically approved by the U.S. Food and Drug Administration ("FDA") to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. These women are at high risk for delivering preterm again – a serious medical condition that is the leading cause of neonatal death in the United States.

2280 Schuetz Road, St. Louis, Missouri 63146 Tel: (314) 645-6600 Fax: (314) 645-3713

As we understand the policy described in the Department's Medicaid Bulletin, a healthcare provider's prescription for Makena® will be approved only if the prescribing provider can furnish clinical justification and medical necessity documentation. Compounded 17P, by contrast, is not subject to these requirements and will be approved so long as the preparation is "compounded in a manner consistent with the FDA's [March 30, 2011] recommendation," with providers required to maintain (but not submit) documentation for potential review from the agency.

We are not certain about what criteria are being applied in assessing clinical justification and medical necessity for Makena® prescriptions. However, we are concerned that the Department appears to have created an arbitrary standard that provides unfettered discretion to determine whether a physician has furnished adequate clinical justification or has adequate medical necessity documentation to permit Makena® coverage. In fact, SCDHHS has routinely denied coverage for Makena® to underprivileged women in South Carolina in favor of an unapproved compounded preparation of 17P, while FDA-approved Makena® is readily available to mothers who have commercial insurance.

The policy imposes a barrier for pregnant women who, at their health care practitioner's advice, have concluded that Makena® — the only FDA-approved drug in the therapeutic category — is the best treatment option to reduce her risk for recurrent preterm birth.

Accordingly, the Department's policy does not appear to be a *bona fide* prior authorization process. We believe federal court decisions clearly indicate that prior authorizations in Medicaid are permissible only if they ensure that patients have access to covered drugs that a prescribing physician determines is medically necessary for a Medicaid beneficiary.

The Company is not certain of the Department's rationale for such an approach. However, if the Department has relied upon or otherwise interpreted statements made by the FDA and certain maternal-fetal and obstetrics medical societies, including the American College of Obstetricians and Gynecologists ("ACOG") in March and April of 2011, as supporting the proposition that there is no difference between FDA-approved Makena® and compounded preparations of 17P, we believe such reliance and interpretation is unfounded, particularly in light of new developments in this area.

The FDA has repeatedly stated that outpatient drugs manufactured under good manufacturing practices standards are safer than compounded preparations. For example, FDA Commissioner Hamburg lauded the FDA approval of Makena® in Congressional testimony: "I think it is important and an advance that we have an FDA-approved drug to

prevent pre-term pregnancy and all of its consequent serious medical concerns for both mother and infant." When it came to compounded preparations of 17P, Commissioner Hamburg testified that "while the drug had been available through compounding . . . compounding as a practice has been associated with serious health risks."

Given the documented risks associated with the compounding process, the FDA's March 30, 2011 statement contemplated utilization of compounded preparations of 17P only in limited, patient-specific circumstances. For example, the FDA statement provides, "under certain conditions, a licensed pharmacist may compound a drug product using ingredients that are components of FDA approved drugs **if the compounding is for an identified individual patient based on a valid prescription for a compounded product that is necessary for that patient.**" (emphasis added) In other words, the FDA is indicating that compounded products can be permissible but only when there is a demonstration of their medical need given the existence of an FDA approved drug.

The Department's policy appears to reverse this approach. Thus, it is our understanding that the Department is broadly approving compounded 17P prescriptions without any medical necessity review that would ensure the compounded preparations are being covered in conformance with the FDA statement. By contrast, the Department does not appear to be offering *bona fide* access to Makena®, even though it is the only FDA-approved drug in its therapeutic category, by virtue of its onerous and, in our view, illegal preauthorization process pursuant to which physicians must demonstrate to the satisfaction of the Department that the FDA approved drug is clinically justified and medically necessary over the unapproved preparation.

Further, on October 13, 2011, the relevant medical societies (including ACOG) issued an official clarification that their prior statements:

- "were . . . not meant to suggest that Makena® and compounded 17P are identical products"
- "were not intended to be used by private or public payers as a basis for interfering with a treating physician's medical judgment or denying access to Makena®."

Less than a week later, ACOG's President reiterated that "Makena and compounded drugs are not identical," and that "insurers should follow a doctor's decision regarding the best prescription drug for his patient's health care needs."

On November 8, 2011, FDA also issued a clarification statement. Specifically, FDA reminded "physicians and patients" that:

> [B]efore approving the Makena new drug application, FDA reviewed manufacturing information, such as the source of the API [active pharmaceutical ingredient] used by its manufacturer, proposed manufacturing processes, and the firm's adherence to current good manufacturing practice. **Therefore, as with other approved drugs, greater assurance of safety and effectiveness is generally provided by the approved product than by a compounded product.** (emphasis added)

As I am sure you are aware, FDA approval is of critical importance to physicians and patients; the compounding process for unapproved drugs has historically resulted in a significant percentage of potency failures and other problems. Worse still, it is our understanding that the unapproved compounded 17P products are frequently made with ingredients manufactured in factories in China that are uninspected and unregulated by the United States government. Independent laboratories, engaged by the Company, have tested samples of the active pharmaceutical ingredients made by those factories, as well as samples of finished compounded 17P products from multiple pharmacies in multiple states, and found that many of them failed the quality and potency standards that apply to FDA-approved Makena®. This obviously raises substantial concerns about the safety and efficacy of the compounded 17P administered to South Carolina Medicaid patients. The FDA is currently investigating the findings made by these independent laboratories.

As you know, in addition to requirements specifically relating to coverage of prescription drugs, Federal Medicaid requirements more generally include provisions governing the provision of high quality care and consideration of the interests of beneficiaries. We urge the Department to reassess how its policy is consistent with those requirements when the policy results in many low-income, pregnant women at high-risk for preterm birth being unable to access an approved product that can meet their medical need, while at the same time apparently encouraging the use of unapproved products of uncertain quality and potency that the Federal government has stated have a greater risk of contamination and less assurance of safety. We also respectfully ask the Department to consider how limiting access to an FDA-approved drug for reducing the risk of preterm birth is consistent with South Carolina's Birth Outcomes Initiative.

The Company is aware that most Medicaid beneficiaries in South Carolina are enrolled in managed care plans. However, it is the State's obligation to establish a policy that ensures beneficiaries have access to prescription drugs consistent with Federal Medicaid requirements, regardless of how the beneficiaries receive their coverage. To the extent the Department — through its prior authorization policy or otherwise — is effectively authorizing denials of all access to Makena®, it has created a "two-tiered system" under which poor

pregnant women eligible for Medicaid are *precluded* from access to the only FDA-approved therapy for this high-risk condition and instead are forced to use an unapproved compounded preparation, while women with private insurance have ready access to the FDA-approved therapy.

I urge you to recognize the potential harm to pregnant women who are denied access to Makena®, a medication that is prescribed by their health care practitioner and to which the Company believes they are entitled under Federal Medicaid requirements. We support the Department's January 6, 2012 announcement regarding the Birth Outcomes Initiative and its goal to work with stakeholders to make it easier for patients to access an affordable progesterone treatment, which we hope means a proven and FDA approved treatment that can help reduce preterm births. We hereby request a meeting with the Department at its earliest convenience to discuss these important matters in the hope of resolving them in a prompt manner consistent with federal law. The Company has previously offered a substantial supplemental rebate to the State, which was declined, and we are prepared to revisit that discussion.

Sincerely,

Gregory J. Divis, Jr.
President & Chief Executive Officer
K-V Pharmaceutical Company

Enclosures: 2

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

Society for Maternal-Fetal Medicine

Information Update on 17α–Hydroxyprogesterone Caproate (17P) from The American College of Obstetricians and Gynecologists and The Society for Maternal-Fetal Medicine

On April 1, 2011, The American College of Obstetricians and Gynecologists ("the College") and the Society for Maternal-Fetal Medicine ("SMFM") with other medical and clinician groups issued a statement regarding Makena™ and compounded 17α-hydroxyprogesterone caproate (17P). The College and SMFM issued an additional statement on April 28, 2011, in response to the numerous questions the organizations had received about the implications of prescribing compounded 17P ("the Statements").

The College and SMFM have been made aware that parts of the Statements may have been taken out of context and used to interfere with physician judgment in prescribing for patients. The Statements were not intended to be used by private or public payers as a basis for interfering with a treating physician's medical judgment or denying patient access to Makena™. The Statements were also not meant to suggest that Makena™ and compounded 17P are identical products. As a result, the College and SMFM are providing the following information:

- Physicians should be permitted to prescribe drugs based upon medical considerations and patient need and access.
- Physicians should be able to prescribe Makena™ or compounded 17P based on accepted medical indications after discussion with the patient.
- Physicians prescribing Makena™ or compounded 17P should be aware of the U.S. Food and Drug Administration's (FDA) statement on Makena™ (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm249025.htm).
- Physicians should understand the inherent differences between an FDA-approved manufactured product and a compounded preparation (See: ACOG Committee Opinion No. 387 Pharmaceutical Compounding, November 2007, http://www.acog.org/partners/greenjournal/co387.pdf).

Furthermore, it has been the College and SMFM's understanding, based upon peer-reviewed published articles, that some of the drugs from the studies used to obtain FDA approval of Makena™ were compounded. The College and SMFM would like to clarify that the study drugs were manufactured in compliance with FDA guidelines for Good Manufacturing Practices.

Date: October 13, 2011

FDA STATEMENT

For Immediate Release: November 8, 2011
Media Inquiries: Shelly Burgess, 301-796-4651, shelly.burgess@fda.hhs.gov

FDA Statement on Makena

FDA approved Makena (hydroxyprogesterone caproate) in February 2011 for the reduction of the risk of certain preterm births in women who have had at least one prior preterm birth. For many years before Makena was approved, a version of the active ingredient of Makena has been available to patients whose physicians requested the drug from a pharmacist who compounded the drug. In March 2011, after learning that the owner of Makena, K-V Pharmaceuticals, had sent letters to pharmacists indicating that FDA will no longer exercise enforcement discretion with regard to compounded versions of Makena, FDA issued a statement about compounded hydroxyprogesterone caproate to clarify the agency's enforcement priorities. In the March 2011 statement, FDA explained that the agency prioritizes enforcement actions related to compounded drugs using a risk-based approach, giving the highest enforcement priority to pharmacies that compound products that are causing harm or that amount to health fraud. The agency also stated:

> In order to support access to this important drug, at this time and under this unique situation, FDA does not intend to take enforcement action against pharmacies that compound hydroxyprogesterone caproate based on a valid prescription for an individually identified patient unless the compounded products are unsafe, of substandard quality, or are not being compounded in accordance with appropriate standards for compounding sterile products. As always, FDA may at any time revisit a decision to exercise enforcement discretion.

In October 2011, FDA received information from K-V Pharmaceuticals regarding the potency and purity of samples of bulk hydroxyprogesterone caproate active pharmaceutical ingredients (APIs) and compounded hydroxyprogesterone caproate products. According to the analysis of this information provided by K-V, there is variability in the purity and potency of both the bulk APIs and compounded hydroxyprogesterone caproate products that were tested. Although FDA has not validated or otherwise confirmed the analyses provided by K-V, FDA has carefully reviewed the data and will conduct an on-site review of the laboratory analyses.

FDA has begun its own sampling and analysis of compounded hydroxyprogesterone caproate products and the bulk APIs used to make them. That process is ongoing. In the meantime, we remind physicians and patients that before approving the Makena new drug application, FDA reviewed manufacturing information, such as the source of the API used by its manufacturer, proposed manufacturing processes, and the firm's adherence to current good manufacturing practice. Therefore, as with other approved drugs, greater assurance of safety and effectiveness is generally provided by the approved product than by a compounded product.

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Brenda James - Log #000319

From: Marie Brown
To: Brenda James
Date: 02/24/2012 3:51 PM
Subject: Log #000319

Hi Brenda,

Per Rick's request, please grant us an extension until March 7, 2012 to respond, due to Mr. Assey being out of the office and Rick will be out of the office next week. Thanks.

Marie A. Brown
Administrative Coordinator
Office of General Counsel
1801 Main Street, 6th Floor
P.O. Box 8206
Columbia, SC 29202-8206
Phone: (803) 898-2795
Fax: (803) 255-8210

Log #000319

South Carolina Department of Health & Human Services

Anthony E. Keck, Director
Nikki R. Haley, Governor

March 22, 2012

Mr. Gregory J. Divis, Jr.
K-V Pharmaceutical Company
2280 Schuetz Road
St. Louis, Missouri 63146

Re: Makena®

Dear Mr. Divis:

We appreciate the opportunity, on March 7, 2012, to meet with two of your representatives, Joseph Auci and Raymond Rodreguez-Torres to discuss South Carolina's position regarding coverage of Makena®. We had a very frank and informative discussion. We also appreciate the interest these gentlemen showed in our Birth Outcomes Initiative and welcome their continued involvement.

The South Carolina Medicaid Program includes coverage of prescribed drugs as allowed by Title XIX (Medicaid) of the Social Security Act. As you know, the Medicaid statutes in the Social Security Act, at 1927(d), allow the Medicaid agency to put reasonable limitations on the coverage of outpatient drugs and require prior authorization for coverage. *See also*, 42 CFR §440.230(d) ("The agency may place appropriate limits on a service based on such criteria as medical necessity. . .").

In accordance with these provisions South Carolina has, through the attached Bulletin, implemented a prior authorization process for prescriptions for Makena®. An individual prescription for compounded 17 Alpha Hydroxyprogesterone Caproate (17-P) does not require a prior authorization. The prior authorization request for Makena® must contain clinical justification and documentation of medical necessity. Thus, contrary to your assertion that SCDHHS' policy denies pregnant women access to Makena®, Makena® is available to women on South Carolina Medicaid provided their doctors submit clinical justification and documentation showing the commercial preparation is medically necessary.

I also want to assure you your statement that "SCDHHS has routinely denied coverage for Makena® to underprivileged women in South Carolina" is incorrect as SCDHHS has received no documented requests for coverage of Makena® for an individual. Therefore, no denials, and certainly no routine denials, have been issued.

Office of the Director
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Finally, as of today's date, SCDHHS is not aware of and has not been provided any official documentation showing that compounded 17-P to fill an individually issued prescription for the compounded preparation is unsafe or that Makena® is more clinically effective. Communications from CMS and the FDA support that assertion. We recognize that the FDA is conducting reviews of these policies and may revise their stance. However, absent any official notification that compounded 17-P is unsafe or inferior to Makena®, SCDHHS will continue to approve requests for compounded 17-P. At the same time, SCDHHS will evaluate requests for Makena®, if any, through its established prior authorization process.

Sincerely,

Anthony E. Keck
Director

AEK/shh

Enclosure

cc: Tim Rogers
Angie Stoner

South Carolina
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Post Office Box 8206
Columbia, South Carolina 29202-8206
www.scdhhs.gov

May 18, 2011

Phys Hosp.
MC Pharm

MEDICAID BULLETIN

TO: **Providers Indicated**

SUBJECT: **17 Alpha Hydroxyprogesterone Caproate**

In February 2011, the Food and Drug Administration (FDA) issued approval for Makena™, a commercially produced 17-alpha hydroxyprogesterone caproate (17-P) product. The FDA issued guidance on March 30, stating that "it does not intend to take enforcement action against pharmacies that compound hydroxyprogesterone caproate based on a valid prescription for an individually identified patient unless the compound products are unsafe, of substandard quality, or are not being compounded in accordance with appropriate standards for compounding sterile products." The South Carolina Board of Pharmacy has indicated a similar position.

The South Carolina Department of Health and Human Services (SCDHHS) will continue to reimburse providers for the use of compounded 17-P that is compounded in a manner consistent with the FDA's recommendation. Reimbursement for the compounded product will be paid at the rate of $20 per unit (250mg injection). Providers should continue to bill using the Healthcare Common Procedure Coding System (HCPCS) code J3490 (unclassified drug) with the TH modifier. Coverage is available beginning at 16 weeks gestation, continuing through 36 weeks for patients with a history of a prior preterm delivery. Other risk factors for preterm delivery do not qualify for reimbursement by SCDHHS.

Prior authorization will not be required for compounded 17-P, but providers are required to maintain documentation in each patient's medical record for potential review from the agency's Program Integrity Division. However, SCDHHS will require prior authorization for any prescription for Makena™, and the physicians must provide clinical justification and medical necessity documentation.

If you have any questions regarding this bulletin, please contact your Program Manager at (803) 898-2660. Thank you for your continued support and participation in the South Carolina Medicaid Program.

/S/
Anthony E. Keck
Director

**NOTE: To receive Medicaid bulletins by email, please register at http://bulletin.scdhhs.gov/.
To sign up for Electronic funds Transfer of your Medicaid payment, please go to:
http://www.dhhs.state.sc.us/dhhsnew/hipaa/index.asp and select "Electronic funds Transfer (EFT)" for instructions.**