IMPORTANT REMINDER
The purpose of this Clinical Policy is to provide a guide to medical necessity reviews for Makena under the pharmacy and medical benefit. Clinical policies are intended to be reflective of current scientific research and clinical thinking. This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.

Subject
Prior authorization of Makena® (hydroxyprogesterone caproate injection) for the prevention of recurrent pre-term delivery.

Description
The intent of the criteria is to ensure that patients follow selection elements established by Superior HealthPlan policy, this policy will be required for coverage of Makena under the medical and pharmacy benefit. Superior HealthPlan follows the guidance of the Texas Vendor Drug Program (VDP) for all Medicaid clinical edit criteria for pharmacy benefit claims. This VDP clinical edit is voluntary and a Managed Care Organization (MCO) is permitted to relax the edit but not be more strict than the edit. Superior has adjusted the clinical criteria to ease the prior authorization process regarding this clinical edit. The criteria question requiring age 16 or older has been removed and the allowable time to start therapy has been extended. That same relaxed criteria for the pharmacy benefit is then extended to medical benefits to allow homogeneity of criteria.

FDA Approved Indications
Makena is indicated to reduce the risk of preterm birth in women with a singleton pregnancy and a history of singleton spontaneous preterm birth. Makena is not intended for use in women with multiple gestations or other risk factors for preterm birth.5
Policy and Procedure

| DEPARTMENT: Pharmacy Operations, Medical Directors | DOCUMENT NAME: Makena Clinical Criteria for Authorization via Pharmacy and Medical Benefit |
| PAGE: 2 of 8 | REPLACES DOCUMENT: |
| APPROVED DATE: 06/01/2015 | RETIRED: |
| EFFECTIVE DATE: 06/01/2015 | REVIEWED/REVISED: 03/16, 11/16, 09/20/17, 9/2018, 6/2019 |
| PRODUCT TYPE: STAR, STAR HEALTH, CHIP, STAR PLUS, STAR Kids | REFERENCE NUMBER: TX.PHAR.15 |

Policy/Criteria

It is the policy of Superior HealthPlan that Makena is medically necessary in the prevention of preterm delivery for women who meet the following criteria as applied to the medical and pharmacy benefit.

Please note, approval prior to 16 weeks gestation: Makena requests may be submitted for approval just prior to 16 weeks, 0 days gestation to allow time for the prior authorization approval process and shipping from the pharmacy.

I. Approval Criteria

1. Does the Member have a diagnosis of singleton pregnancy?
   [ ] Yes (Go to #2)
   [ ] No (Deny)

2. Does the Member have a history of spontaneous singleton preterm birth? Defined as a singleton live birth at age 16 weeks 0 days to 36 weeks 6 days or stillbirth before 24 weeks presenting as labor, ruptured membranes or advanced cervical dilation or effacement.3
   [ ] Yes (Go to #3)
   [ ] No (Deny)

3. Is the Member between 16 weeks 0 days and 27 weeks 6 days gestation?
   [ ] Yes (Go to #4)
   [ ] No (Deny)

4. Does the Member have a history of any of the following: thromboembolic disorders, known or suspected breast cancer, abnormal vaginal bleeding unrelated to pregnancy, cholestatic jaundice of pregnancy, liver tumors or active liver disease and/or uncontrolled hypertension?
   [ ] Yes (Deny)
   [ ] No (Go to #5)

5. Is the Member using less than or equal to (≤) 250mg intramuscularly (IM) or 275mg subcutaneously (SQ) weekly?
   [ ] Yes (Approve for weekly Makena injections to begin between 16 weeks and 27 weeks 6 days and continue through 36 weeks 6 days gestation OR delivery, whichever comes first)
   [ ] No (Deny)
*This policy is adapted from Texas Vendor Drug Program Makena criteria. The original clinical edit can be located at [https://paxpress.txpa.hidinc.com/makenapdg.pdf](https://paxpress.txpa.hidinc.com/makenapdg.pdf). We are providing the drug for more members than the VDP would permit therefore we operationalize the approval period to reflect appropriate dosing parameters.
**Makena Algorithm**

1. **Does the client have a history of spontaneous singleton preterm birth?** Defined as a singleton live birth at age 16 weeks 0 days to 36 weeks 6 days or stillbirth before 24 weeks presenting as labor, ruptured membranes or advanced cervical dilation or effacement.
   - **Yes**
   - **No**

   - **No**
     - **Denied**
     - **Yes**
       - **Denied**
       - **Yes**
         - **Denied**
         - **Yes**
           - **Denied**
           - **Yes**
             - Approved - for weekly Makena injections to begin between 16 weeks and 27 weeks 6 days and continue through 36 weeks 6 days gestation OR delivery, whichever comes first

2. **Is the client between 16 weeks 0 days and 27 weeks 6 days gestation?**
   - **Yes**
   - **No**

   - **No**
     - **Denied**
     - **Yes**
       - **Denied**
       - **Yes**
         - **Denied**
         - **Yes**
           - **Denied**
           - **Yes**
             - Approved - for weekly Makena injections to begin between 16 weeks and 27 weeks 6 days and continue through 36 weeks 6 days gestation OR delivery, whichever comes first

3. **Does the client have a history of any of the following: thromboembolic disorders, known or suspected breast cancer, abnormal vaginal bleeding unrelated to pregnancy, cholestatic jaundice of pregnancy, liver tumors or active liver disease and/or uncontrolled hypertension?**
   - **Yes**
   - **No**

   - **No**
     - **Denied**
     - **Yes**
       - **Denied**
       - **Yes**
         - **Denied**
         - **Yes**
           - **Denied**
           - **Yes**
             - Approved - for weekly Makena injections to begin between 16 weeks and 27 weeks 6 days and continue through 36 weeks 6 days gestation OR delivery, whichever comes first

4. **Is the client using less than or equal to (≤) 250mg intramuscularly (IM) or 275mg subcutaneously (SQ) weekly?**
   - **Yes**
   - **No**

   - **No**
     - **Denied**
     - **Yes**
       - **Denied**
       - **Yes**
         - **Denied**
         - **Yes**
           - **Denied**
           - **Yes**
             - Approved - for weekly Makena injections to begin between 16 weeks and 27 weeks 6 days and continue through 36 weeks 6 days gestation OR delivery, whichever comes first
Safety

Background
Makena works as a long acting progestin when administered intramuscularly. Although the exact mechanism by which Makena reduces the risk of preterm birth is unknown, mechanisms of endogenous progesterone include relaxation of uterine smooth muscle, blocking the action of oxytocin, and maintenance of pregnancy.10

Preterm birth is defined as birth occurring before 37 weeks gestation and it occurs in approximately 12% of all live births in the US. It is a leading cause of infant death and long-term disability. Preterm birth related healthcare costs reached approximately $26 billion in 2005. Women who have had a spontaneous preterm delivery are at a greatly increased risk for preterm delivery in subsequent pregnancies. The earlier in the pregnancy a preterm delivery occurs, the greater the chance of preterm delivery in a subsequent pregnancy.9

Studies have shown that administration of a weekly intramuscular injection of 17-alpha-hydroxyprogesterone caproate (17P) in patients with a previous spontaneous singleton preterm delivery resulted in a significant reduction in the rate of recurrent preterm delivery and decreased neonatal intensive care unit admissions. The studies demonstrating the greatest benefit show that 17P should be initiated between 16 and 20 6/7 weeks gestation. Studies have shown some benefit with initiation up to ≤ 27 6/7 weeks gestation, but the likelihood of preventing an early premature delivery is reduced and the current FDA labeled indication is for initiation between 16-20 6/7 weeks.11 Superior will allow the prolonged window to start the drug. There is no current evidence to support starting 17P after 28 weeks gestation.2,4,6,7,8 Makena should be considered an option to reduce the risk of premature birth in singleton gestation women with a history of spontaneous preterm singleton birth.1,11 It should be initiated between 16 and 20 6/7 weeks gestation and continued until 36 6/7 weeks gestation or delivery, whichever occurs first.12

Carefully monitor for and consider recommendations if any of the following conditions occur during use:5

<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolic events</td>
<td>Discontinue Makena</td>
</tr>
<tr>
<td>Allergic reactions (urticaria, pruritus, angioedema)</td>
<td>Consider discontinuing Makena</td>
</tr>
<tr>
<td>Decreased glucose tolerance</td>
<td>Monitor in pre-diabetic and diabetic women</td>
</tr>
<tr>
<td>Fluid retention</td>
<td>Monitor in women with conditions that may be adversely effected by fluid retention (cardiac or renal dysfunction, preeclampsia, epilepsy, migraine, asthma)</td>
</tr>
</tbody>
</table>
Depression Monitor in women with a history of depression. Discontinue Makena if depression recurs.

Jaundice Monitor and consider benefits vs. risk of continuing treatment

Hypertension Monitor women who develop hypertension while receiving Makena and consider benefits vs. risks of continuing

References


References for Additional Information


**Policy and Procedure**

<table>
<thead>
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<tr>
<th><strong>Revision Log</strong></th>
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<tbody>
<tr>
<td>Added statement to allow processing just prior to gestational week 16 day 0</td>
<td>10/15</td>
</tr>
<tr>
<td>Added statement to “criteria as applied to the pharmacy benefit” to the Policy/Criteria section</td>
<td>03/16</td>
</tr>
<tr>
<td>Removed Gayle Dichter and added Justin M. Weiss on Approval</td>
<td>11/16/2016</td>
</tr>
<tr>
<td>Added STAR Kids to Product Type</td>
<td>11/16/2016</td>
</tr>
<tr>
<td>Changed Makena algorithm to allow injections to begin up to 27 6/7 weeks gestation</td>
<td>09/20/2017</td>
</tr>
<tr>
<td>Added “David” to Dr. David Harmon as an approver</td>
<td>09/2017</td>
</tr>
<tr>
<td>Added “and Medical” to the name and body of document. Updated Makena algorithm to condense content of boxes 4 and 5 to a single box</td>
<td>09/2018</td>
</tr>
<tr>
<td>Updated Policy/Criteria and Makena Algorithm sections to reflect VDP guidance. VDP permits the criteria to be voluntary and thus less strict than VDP has written. Age edit on VDP criteria omitted. Lengthened window to start Makena is approved per PA. Also defined previous spontaneous birth for internal reference. Updated description section regarding applying criteria to medical and pharmacy benefit. Updated references to include TX VDP criteria references, ACOG and Iams article added. Removed Justin Weiss and added Karen Tadlock on Approval</td>
<td>6/2019</td>
</tr>
</tbody>
</table>

**POLICY AND PROCEDURE APPROVAL**

*The electronic approval retained in RSA Archer, Centene’s P&P management software, is considered equivalent to a physical signature.*

Karen Tadlock, V.P., Pharmacy Operations Approval on file
Dr. David Harmon, Sr. V.P., Chief Medical Officer Approval on file
Pharmacy & Therapeutics Committee: Approval on file