Use of Hydroxyprogesterone Caproate and Progesterone During the 2\textsuperscript{nd} and/or 3\textsuperscript{rd} Trimester Among Pregnancies with Live Birth Deliveries in the Sentinel Distributed Database

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Clinical Background

• Preterm birth (PTB) occurs in ~10% of all births, resulting in neonatal mortality and morbidity.

• To date, no drugs are approved for reducing neonatal morbidity and mortality associated with PTB.

• Progesterone has been used off-label to prevent PTB

• Makena® (hydroxyprogesterone caproate injection, HPC) is the only product approved for reducing the risk of recurrent PTB.
Regulatory History

• Makena received accelerated approval in 2011. Full approval is contingent upon a successful confirmatory trial to verify its clinical benefit in improving neonatal morbidity and mortality.

• The confirmatory trial (PROLONG) completed in 2018 showed Makena had no clinical benefit and failed to reduce the risk of recurrent PTB.

• FDA convened an Advisory Committee (AC) meeting in 2019 to discuss the evidence on Makena's efficacy and to inform FDA’s regulatory decision-making for this product.
Sentinel Study Objectives

To inform AC members on the utilization and reasons for Makena use, we initiated a Sentinel analysis with the following objectives

1) **Drug utilization:**
   To determine the percentage of live-birth pregnancies used injectable HPC or progesterone during 2\textsuperscript{nd} and/or 3\textsuperscript{rd} trimesters

2) **Possible reasons for use:**
   To determine the percentage of live-birth pregnancies used injectable HPC or progesterone that also had at least one obstetrical condition related to PTB
Methods

• **Database**: Sentinel Distributed Database
  - Primarily composed of commercially-insured patients

• **Population**: Women with live-birth deliveries b/w Jan 2008 - Apr 2019
  - Pregnancy duration and trimester periods are estimated using a validated algorithm

• **Medications of interest**: HPC and progesterone
  - Ascertained through NDC and HCPCS codes
  - HPC in injectable or bulk powder formulation
  - Progesterone in vaginal, oral, injectable, or bulk powder formulation
Related obstetrical conditions (possible reasons for use)

- Identified by ICD-9 and ICD-10 codes in inpatient or outpatient records
  - Narrow definition:
    - Preterm delivery in a **prior** pregnancy
    - Preterm labor in a **current** pregnancy
    - Cervical shortening in a **current** pregnancy
  - Broad definition:
    - Same three obstetrical conditions above recorded in a **prior pregnancy or the current pregnancy**
Temporal Trend on Number of Pregnancies With injectable HPC Use Per 1,000 Pregnancies

- Total Live-Birth Pregnancies: 3,451,121

1 Data from 2019 was incomplete and excluded from the figure
Most Injectable HPC Users Had a Related Obstetrical Diagnosis Code

<table>
<thead>
<tr>
<th>Related Obstetrical Conditions</th>
<th>Injectable HPC (N=16,535)</th>
<th>Progesterone (N=40,144)</th>
<th>Any HPC or Progesterone (N=61,615)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Narrow Definition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Preterm delivery in a past pregnancy</td>
<td>39%</td>
<td>11%</td>
<td>20%</td>
</tr>
<tr>
<td>2. Preterm labor in a current pregnancy</td>
<td>49%</td>
<td>45%</td>
<td>47%</td>
</tr>
<tr>
<td>3. Cervical shortening in a current pregnancy</td>
<td>20%</td>
<td>32%</td>
<td>27%</td>
</tr>
<tr>
<td>Any of the conditions above</td>
<td>73%</td>
<td>61%</td>
<td>65%</td>
</tr>
<tr>
<td><strong>Broad Definition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Preterm labor or delivery in a past pregnancy</td>
<td>95%</td>
<td>37%</td>
<td>56%</td>
</tr>
<tr>
<td>2. Preterm labor or delivery in a current pregnancy</td>
<td>54%</td>
<td>55%</td>
<td>56%</td>
</tr>
<tr>
<td>3. Cervical shortening in a past or current pregnancy</td>
<td>24%</td>
<td>33%</td>
<td>29%</td>
</tr>
<tr>
<td>Any of the conditions above</td>
<td>98%</td>
<td>75%</td>
<td>83%</td>
</tr>
</tbody>
</table>
Limitations

– Might not be generalizable to women without a commercial health plan

– Unspecified timing between related obstetrical conditions and injectable HPC use

– Inability to capture medication use paid for by patients as they are not billed to health plans
Conclusions

- In the Sentinel Distributed Database
  - Overall modest use of HPC (~1.3% in 2018) and progesterone (~1.4% in 2018) during 2\textsuperscript{nd} or 3\textsuperscript{rd} trimesters in live-birth pregnancies
  - Most (at least 73%) of the pregnant women using injectable HPC had a related obstetrical condition recorded before or during the current pregnancy.
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