Accutane and Pregnancy Exposure

9/18/2000

Regulatory History Accutane

- 1982
  - Accutane approved as: Pregnancy Category X
  - Label described risk of teratogenicity
    - Contraindications
    - Warnings
    - Precautions
  - *Patient Information Brochure* also contained warnings about avoiding pregnancy
Regulatory History Accutane

• 1983
  – First report of infant born with malformations
    • Label changes
    • First ‘Dear Doctor’ letter
    • Second ‘Dear Doctor’ letter with additional information about the reported cases
  – Sponsor distributes red stickers to pharmacies with further warnings

• 1984
  – Labeling changes
  – Third ‘Dear Doctor’ letter

• 1984 to 1988
  – Roche issued seven ‘Dear Doctor’ letters

• 1988
  – Advisory Committee Meeting
  – Roche introduced the concept of the Accutane Pregnancy Prevention Program (PPP)
Accutane PPP

- Boxed Warning
- Informed Consent for Female Patients
- Warnings on Package
- PPP Kit for Prescribers
- Multiple Other Educational Efforts
- Accutane Tracking Study
- Patient Enrollment Survey (Slone Survey)

Accutane PPP

- Boxed Warning
  - Strict qualifications for Rx to females
  - Pregnancy testing
  - Two reliable methods of contraception
    - 1 month before Tx
    - During Tx
    - 1 month after Tx
  - Instructions to begin Tx on the 2-3 days of next menstrual period
Accutane PPP

- Boxed Warning
  - Negative pregnancy test within one week before starting therapy
  - One month prescription supply
  - Monthly pregnancy testing and monthly contraceptive counseling

Accutane PPP

- Informed Consent for Female Patients
- Warnings on Package
  - Blister packaging with avoid pregnancy sign
Accutane PPP

• PPP Kit for Prescribers
  – Pregnancy Counseling Materials
  – Patient Information Brochure
  – Information on the Patient Referral Program
  – Toll-Free-Number

• Other Educational Efforts
  – CME courses
  – Training video for residency programs

Accutane PPP

• Accutane Tracking Study
  – Evaluates physician’s usage of Roche’s PPP Kit and other core components of the PPP

• Patient Enrollment Survey (Slone Survey)
  – Independent follow-up survey conducted by the Slone Epidemiology Unit at Boston University School of Public Health
Accutane Tracking Study

- **Description**
  - Telephone Survey
  - Includes 110 dermatologists and 200 primary care physicians
- **Purpose**
  - Determine usage of PPP components
- **Limitations**
  - Tracks physicians' perceptions of PPP use rather than actual use

Accutane PPP - Slone Survey

- Voluntary survey of women treated with Accutane since 1989
- Seeks to measure
  - Patient's knowledge of Accutane's teratogenic risk
  - Compliance with PPP components
  - Pregnancy exposure rates of enrollees
  - User profile
    - Risk factors for pregnancy exposure
Accutane PPP - Slone Survey

- Captures 30-40% of women treated with Accutane

Accutane PPP

- Tools to monitor the impact of the PPP on the occurrence of pregnancy exposure
  - Slone Survey
  - Accutane Tracking Study
  - Case Reports
Roche/FDA’s Concerns

- Both Roche and FDA have evaluated this program’s performance and concluded that there are specific areas of the program which need to be strengthened

Areas of Concern

- Patterns of Drug Use
- Performance Characteristics of the PPP
  - Slone Epidemiology Unit Survey Data
  - Accutane Tracking Study
- Case Report Data
Drug Utilization Data

Estimated Number of Patients Treated with Antimycotics by Year 1982-1999

Source: IMS HEALTH, NDTI & NPA Plus and National Data Incorporated
Drug Use Data: Summary

- Use in women approximates use in men
- Accutane use in women has increased > 200% between 1992 and 1999
- 85-90% of women using Accutane are aged 15-44
- Among women 15-44, 80% of use is below age 30
Distribution of Women Enrolled in Slone Survey by Pregnancy Risk Category, 95-99

<table>
<thead>
<tr>
<th>Pregnancy Risk Category</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexually Active</td>
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<tr>
<td>Using Birth Control</td>
<td>39</td>
</tr>
<tr>
<td>Not Using Birth Control</td>
<td>1</td>
</tr>
<tr>
<td>Not Sexually Active</td>
<td>57</td>
</tr>
<tr>
<td>Using Birth Control</td>
<td>25</td>
</tr>
<tr>
<td>Not Using Birth Control</td>
<td>32</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Hysterectomy or Postmenopausal</td>
<td>3</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
</tr>
</tbody>
</table>
## Non-Compliance with Roche’s Pregnancy Prevention Program, 95-99

<table>
<thead>
<tr>
<th>PPP Element</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did Not Report Signing Consent</td>
<td>23</td>
</tr>
<tr>
<td>Did Not Report Having a Pregnancy Test Before TX</td>
<td>25</td>
</tr>
<tr>
<td>Did Not Report Postponing TX for Pregnancy Test Results</td>
<td>33</td>
</tr>
<tr>
<td>Did Not Report Postponing TX to Next Menstrual Period</td>
<td>43</td>
</tr>
<tr>
<td>Did Not Report Having a Pregnancy Test During TX</td>
<td>40</td>
</tr>
</tbody>
</table>

## Accutane Exposed Pregnancies Identified in the Slone Survey, 89-00

<table>
<thead>
<tr>
<th>Exposed Pregnancies</th>
<th>958</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy Outcomes</td>
<td></td>
</tr>
<tr>
<td>Terminations</td>
<td>834</td>
</tr>
<tr>
<td>Elective</td>
<td>644</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>164</td>
</tr>
<tr>
<td>Ectopic</td>
<td>26</td>
</tr>
<tr>
<td>Live Births</td>
<td>110</td>
</tr>
<tr>
<td>Unknown</td>
<td>14</td>
</tr>
</tbody>
</table>
Slone Survey

- Congenital Anomalies
  - Pregnancies resulting in Live Births = 110
  - Total # of infants born = 111*
  - Number of infants with available medical record or who were examined = 60
    - 8/60 (13%) showed major malformations

*Including one set of twins

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Pregnancy Rates Among Slone Survey Enrollees

<table>
<thead>
<tr>
<th>Year</th>
<th>Rate/1,000 person-years</th>
<th>Est.# of Pregnancy Exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>7.8</td>
<td>231</td>
</tr>
<tr>
<td>1992</td>
<td>7.7</td>
<td>244</td>
</tr>
<tr>
<td>1993</td>
<td>7.1</td>
<td>251</td>
</tr>
<tr>
<td>1994</td>
<td>6.2</td>
<td>241</td>
</tr>
<tr>
<td>1995</td>
<td>7.4</td>
<td>342</td>
</tr>
<tr>
<td>1996</td>
<td>7.0</td>
<td>355</td>
</tr>
<tr>
<td>1997</td>
<td>6.3</td>
<td>368</td>
</tr>
<tr>
<td>1998</td>
<td>5.6</td>
<td>359</td>
</tr>
</tbody>
</table>
Slone Survey: Summary

- Pregnancies are still occurring
- Substantial non-compliance with critical elements of Accutane PPP is well documented
- Representativeness of survey unlikely
  - Voluntary, captures less than 40% of all users

Accutane Tracking Study
Accutane Tracking Study Results

- Physicians do not use all the elements included in the kit because:
  - They feel oral communication is adequate
  - Feel kit is inconvenient to them
- High use of product brochure
- Slight increase over time in the report of pregnancy testing and use of consent form

Case Reports
Limitations of Case Reports

- Only a small percentage of adverse drug events are recognized and reported to FDA
- Reporting of adverse drug events typically declines over the marketing history of a drug product
Accutane Pregnancy Exposures, Roche Data 1982-2000

<table>
<thead>
<tr>
<th>Exposed Pregnancies</th>
<th>1,995</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pregnancy Outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>Terminations</td>
<td>1,446</td>
</tr>
<tr>
<td>Elective</td>
<td>1,214</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>213</td>
</tr>
<tr>
<td>Missed</td>
<td>19</td>
</tr>
<tr>
<td>Live Births</td>
<td>383</td>
</tr>
<tr>
<td>Unknown</td>
<td>166</td>
</tr>
</tbody>
</table>

Roche Safety Database 1982-2000

- Congenital Anomalies
  - Pregnancies resulting in Live Births = 383
  - Infants with Congenital Anomalies = 162
    (42%)
**Estimated Rates of Congenital Anomalies in Accutane Exposed Pregnancies Resulting in Births**

<table>
<thead>
<tr>
<th></th>
<th>Congenital Anomaly Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event Reports</td>
<td>42%</td>
</tr>
<tr>
<td>Literature</td>
<td>25%</td>
</tr>
<tr>
<td>Voluntary Survey</td>
<td>13%</td>
</tr>
</tbody>
</table>

**Case Report: Summary**

- Pregnancy exposures reported to Roche and FDA are not declining
- 1,995 exposed pregnancies documented by Roche since approval
  - 1,446 since Accutane® PPP inception
- Congenital anomalies continue to be reported to Roche and FDA
Pregnancy Exposure Model

Step I
- Distribution of Contraceptive Use

Step II
- Contraceptive Failure Rates

Step III
- Estimated # Exposed Pregnancies

Results
- #
  - Slone $<40\%$
    - Perfect Contraceptive Use
    - #
    - Typical Contraceptive Use
    - #
  - NSFG General Population
    - Perfect Contraceptive Use
    - #
    - Typical Contraceptive Use
    - #

1999 Females 15-44 years TX with Accutane
## Model: Summary

- Estimated pregnancy exposures in 1999
  - 700 - Slone Survey contraceptive distribution/perfect use
  - 1,300 - Slone Survey contraceptive distribution/typical use
Conclusions

- Drug use of Accutane among women of childbearing potential is escalating
- In spite of all the Sponsor’s efforts to communicate Accutane’s teratogenic potential there is still limited compliance with
  - Pregnancy testing before exposure
  - Pregnancy testing during exposure
  - Appropriate use of contraception

Conclusions

- Measures of pregnancy exposures and outcomes based on the Slone Survey and spontaneous case reports are not representative
  - Participation in Slone Survey is incomplete (<40%)
- Increasing numbers of women exposed to Accutane increases the absolute number of pregnancy exposures