RIBAVIRIN PREGNANCY REGISTRY

Supported by Aurobindo Pharma USA, Genentech, a member of the Roche Group, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Sandoz Inc., Teva Pharmaceuticals USA, Inc., Kadmon Pharmaceuticals, LLC, Zydus Pharmaceuticals (USA) Inc.
Managed by INC Research.

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Background

Initiatives Impacting Pregnancy Monitoring

- FDA - Pregnancy and Lactation Labeling Rule, effective June 2015
  (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm)
- FDA - Guidelines specifically addressing pregnancy registries (draft 1999, issued 2002)
- FDA - Guidance “Evaluating the Risks of Drug Exposure in Human Pregnancies”
  (see http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071645.pdf)
- CDC/FDA - How to systematically monitor pregnancy exposures to specific products or classes of products (2000)
- HIPAA Regulations (2000, final 2002)

Background *(2)*

- FDA has determined as necessary, post-marketing commitment for certain products, structured programs for monitoring pregnancy exposures be conducted
- FDA determined that Ribavirin Pregnancy Registry meeting *FDA Guidance for Industry: Establishing Pregnancy Exposure Registries (2002)* is necessary as post-marketing commitment for ribavirin as potential teratogen

(see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071639.pdf)

About Ribavirin

- Ribavirin, nucleoside analog, is indicated and approved for use in combination with alpha interferon or pegylated alpha interferon for treatment of chronic hepatitis C (HCV)
- Significant teratogenic and/or embryocidal effects occurred in all animal species exposed to ribavirin. No study data in humans
- FDA Pregnancy Category X with “black box” warning

  Contraindicated in pregnancy. Studies in animals or humans, or investigational or post-marketing reports, have shown fetal risk which clearly outweighs any possible benefit to women who are pregnant and the male partners of women who are pregnant.

Ribavirin Pregnancy Registry

- FDA determined Registry necessary for manufacturers' postmarketing commitment for safety surveillance of ribavirin
- Component of Ribavirin Risk Management program which includes language in prescribing information and medication guides on
  - Need to avoid pregnancy
  - How to avoid pregnancy
- Registry is a program to access feasibility and progress under Scientific Advisory Board oversight

Ribavirin Pregnancy Registry (2)

- Registry prospectively monitors direct and indirect pregnancy exposures to ribavirin
  - Direct through pregnant female patients treated with ribavirin
  - Indirect through pregnant female's male sexual partner treated with ribavirin
- Exposure period: while taking ribavirin or for 6 months after ribavirin stopped

Objectives

Primary Objective

- To evaluate association between pregnancy and birth defects in females exposed to ribavirin during pregnancy or within 6 months after therapy stopped
  - Direct through pregnant female patient treated with ribavirin
  - Indirect through pregnant female's male sexual partner treated with ribavirin

Secondary Objectives

- Attempt to estimate risk of major birth defects following direct or indirect pregnancy exposure to ribavirin
- To detect any increase in the prevalence / pattern of birth defects

Registry Design

- **Prospective, observational, exposure-registration and follow-up program of pregnant females exposed to ribavirin**
  - During pregnancy or who become pregnant within 6 months after therapy stopped
  - Exposure may be either direct or indirect through male sexual partner treated with ribavirin
- Enrollment of pregnant patients into Registry is **voluntary**. Initiated by health care providers and/or pregnant patients or pregnant patient's male sexual partner treated with ribavirin
  - Patient-initiated enrollments must be verified by health care provider (HCP)

Registry Design (2)

Registration and follow-up of pregnant female

- Registration of pregnant female through patient or her health care provider (HCP) as early in pregnancy as possible (before the outcome or perceived outcome is known)
- Follow-up at each trimester and at pregnancy outcome through obstetric HCP

Pediatric follow-up on live births

- Follow up at outcome, 6 and 12 months through infant's pediatric HCP

IRB, Consent, HIPAA

- IRB protocol review and approval (12/03, revised 09/04, 03/10, 5/11, 08/13)
- Included in IRB approval
  - Waiver of informed consent for HCP initiated reports
    - Use Registry-assigned log ID with **no** direct patient identifiers collected
    - For follow-up through outcome of pregnancy through registering HCP
  - Use of Registry Information Sheet rather than informed consent form
    - Patient initiated reports
    - For follow-up for live birth outcomes
  - Waiver of documentation of receipt of information sheet
  - HIPAA doesn't apply

Justification Consent/HIPAA Considerations

- Waiver of informed consent for HCP initiated reports (45 CFR 46.116(d))
  - No more than minimal risk to subjects
  - Waiver will not adversely affect the rights and welfare of the subjects
  - Study not practicable to be conducted without waiver
  - Whenever appropriate, the subjects will be provided with additional pertinent information after participation
- Waiver of documentation (21 CFR 56.109(c)(1))
  - No more than minimal risk
  - No procedures where written consent is normally required
- HIPAA doesn't apply for Registry

Potential Reporters to Registry

- Pregnant female with:
  - Direct exposure to ribavirin (i.e., treated with ribavirin)
  - Indirect exposure to ribavirin (male sexual partner treated with ribavirin)
- Pregnant female's male sexual partner treated with ribavirin
- Health care providers (HCPs)
  - Ribavirin prescribing or HCV treating HCP
  - Obstetric HCP
  - Pediatric HCP (for live birth outcomes)

Registration Contacts

Pregnant female initial contact to Registry

- Directly exposed pregnant female patient
  - Request verbal consent to 1) collect contact information and registration and 2) send information sheet and medical release forms to allow contact with OB HCP and pediatric HCP (for live birth) or collect information verbally
- Indirectly exposed pregnant female
  - Request verbal consent to 1) collect contact information and registration and 2) send information sheet and medical release forms for OB HCP and pediatric HCP (for live birth) or collect information verbally
  - Send data forms, information sheet and medical release forms for male sexual partner exposed to ribavirin to complete (contact prescribing HCP) in addition to pregnant female

Registration Contacts *(2)*

Male sexual partner treated with ribavirin initial contact

- Male sexual partner of pregnant female
  - Request verbal information sheet to 1) collect contact information and exposure and family history and 2) send information sheet and medical release forms for prescribing HCP and for exposed pregnant partner
  - Send data forms, information sheet and medical release forms for exposed pregnant partner (to contact OB HCP and for live birth, pediatric HCP) and exposed male

Registration Contacts *(3)*

Non-OB HCP initial contact for:

- Male sexual partner treated with ribavirin of pregnant female (indirect exposure)
  - Have HCP ask exposed male to contact Registry or
  - Send HCP data forms, information sheet, and medical release form packets for both male and his exposed pregnant partner
- Pregnant female patient treated with ribavirin (direct exposure)
  - Have HCP ask patient to contact Registry or
  - Send HCP data forms, information sheet, and medical release form packets for the patient

Registration Contacts *(4)*

HCP initial contact

- Assign patient a log ID (used to identify the patient for follow-up through outcome)
- No direct patient identifiers collected
- Complete registration over phone or send data forms to HCP to complete
- At outcome (if live birth likely) send HCP information sheet and medical release forms to allow contact with infant's pediatric HCP

Registration & Data Collected

Obstetric Healthcare Provider

- As early in pregnancy as possible
  - Age, LMP, EDD, race/ethnicity
  - Family obstetrical history (maternal and paternal)
- At registration and updated at follow-up
  - Ribavirin, other medications, and clinical conditions
  - Prenatal tests (type, date, results)
  - Tobacco and alcohol use

Registration & Data Collected (2)

Ribavirin Prescribing Healthcare Provider

- At enrollment
  - Ribavirin exposure information (for male or female treated with ribavirin)
  - Pregnancy family history (male exposure only, female through OB HCP)

Follow-Up & Data Collected

Obstetric Healthcare Provider

- At each trimester following enrollment: Update information collected at Registration
  - Other medications, and clinical conditions
  - Prenatal tests (type, date, results)
  - Tobacco and alcohol use
- At outcome
  - Outcome – live birth, stillbirth, spontaneous or elective abortion
  - Date of outcome or gestational age at outcome
  - Gender, length, weight, head circumference, APGAR scores
  - If defects identified, details of birth defect

Follow-Up & Data Collected (2)

Pediatric Healthcare Provider

- At outcome
  - Date of outcome or gestational age at outcome
  - Gender, length, weight, head circumference, apgar scores at birth
  - If birth defects identified, details of birth defect
- At 6 and 12 months
  - Infant age, length, weight, head circumference
  - If birth defects identified, details of new birth defects, update on defects identified previously

Scientific Advisory Board

Important feature of Registry – Scientific Advisory Board

- Members from academia, government agencies, pharmaceutical industry with expertise in hepatitis, maternal fetal medicine, teratology, epidemiology
- Organization
  - Executive Committee – voting members, meet for final independent discussion and vote
  - Government Agency members – *ex officio,* non-voting members
  - Sponsor Committee – *ex officio,* non-voting members
- Activities
  - Review of Registry reports of birth defects and aggregate data
  - Development and update of Registry Interim Report to FDA
  - Determine timing, appropriateness, content of Registry Progress Reports
  - Assist in raising awareness of Registry (presentation, materials, etc.)

Steering Committee

Organization

- Sponsor Committee (voting members)
- Chair of Scientific Advisory Board (non-voting)
- Coordinating Center (non-voting)

Activities

- Fiscal decisions (budgets, any new activities suggested by Board or Sponsors)
- Oversight of Registry Management
- Discuss / resolve operational issues of Registry
- Raise awareness about Registry & Risk Management Program

Coordinating Center

Contract organization conducting Registry for Sponsors

- Program/Project management
- As Principle investigator, IRB submissions / interactions
- Enrollment/ case/ AE/ SAE/ Birth defect management
- Single point of contact for Board and Sponsors
- Meeting organization (Scientific Advisory Board/ Steering Committee/ Sponsor)
- Registry reports/ materials generation and distribution
- Registry Interim Report submission to FDA
- Awareness activities (e.g., website)
- Data Management
- Analysis and report generation

Comparison Groups

- MACDP (Metropolitan Atlanta Congenital Defects Program)
- APR (Antiretroviral Pregnancy Registry)
- Identify other groups, as appropriate and available

Birth Defect Evaluation

- Use MACDP criteria for birth defect
- Coding system developed for APR by Scheuerle (2002)
- Evaluation process similar to APR
  - Each report of birth defect evaluated by Scientific Advisory Board primary evaluator(s)
    - Review and evaluation of birth defect report
    - Coding of birth defects
    - Determination of temporality assessment
  - Evaluation and agreement by members of Scientific Advisory Board

Pregnancies with Outcomes (Feb 2016)

Maternal Demographics at Registration – Analysis Population – Valid Prospective U.S. Non-clinical Trial Registry Cases with an Outcome Reported Through 09 February 2015

	Ribavirin Exposure Source Overall	
Pregnancies Enrolled	272	
Age (years)		
n	233	
Mean (SD)	29.7	(6.28)
Median (Interquartile Range)	29.0	(24.0 – 35.0)
Min, Max	18 – 47	
Missing	39	
Race/Ethnicity		
White	160	(58.8%)
Black	20	(7.4%)
Hispanic	24	(8.8%)
Asian	6	(2.2%)
Other	10	(3.7%)
Missing	52	(19.1%)
Clinical Conditions		
HCV	133	(48.9%)
HIV	0	
None (indirect exposure)	99	(36.4%)
Missing	40	(14.7%)

Summary

- Ribavirin Pregnancy Registry is voluntary prospective, exposure-registration and follow up program
- Follow up during pregnancy, at outcome and for 12 months following live birth
- Prospective enrollments may be initiated by:
  - Pregnant patient with direct or indirect exposure to ribavirin during treatment or for 6 months after treatment stopped
  - Male sexual partner (treated with ribavirin) of pregnant female
  - Through HCPs (prescribing, obstetric, genetic counselor, etc.)
- Registry looks for ways to enhance Registry reporting and opportunities increase awareness of Registry

Contacting the Registry

Ribavirin Pregnancy Registry
1011 Ashes Drive
Wilmington, NC 28405

800-593-2214 (toll-free phone)
800-800-1052 (toll-free fax)
www.RibavirinPregnancyRegistry.com (website)
pregnancyregistries@INCResearch.com (email)