Electronic Mail Message

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Date: 08/29/2000 5:34:36 PM
From: Amarilys Vega (VEGAA)
Subject: RE: Additional Accutane Pregnancy Comments

Marty,

Thanks a lot for the update.
I'm working on those changes.

I'm intrigued by the significant differences between our AERS numbers and Roche's numbers since we are supposed to have all the reports they have (with the exception of the periodic reports after the transition of SRS to AERS in 1997). So, why couldn't we capture all those reports the company sent us when we searched AERS? Also, the company reports that most of the abortions were elective abortions but, AERS data shows that the largest numbers of abortions were spontaneous abortions. I need to find out how are they (Roche) coding their cases and if all SLONE reports are sent to us.

Lisy

Electronic Mail Message

Date: 10/20 2001 4:34:47 PM
From: Julie Beitz BEITZJ
Subject: Re: Accutane ADF Letter

Folks,

Please comment on the attached draft letter regarding reporting of pregnancy outcomes. We have determined that the shortfall in reports in AERS was due to the fact that approximately 1200 or so were submitted only as study reports (in Slone's quarterly reports) not as 15-day or periodic reports. Mac suggested that we request that these be sent in the periodic reports and labeled serious so that they will be captured in AERS.

Julie

NDA 18-662

Hoffmann-La Roche Inc
Attention: John La Flore, MD
Vice President, Drug Safety & Risk Management
340 Kingsland Street
Nutley, New Jersey 07110-1199

October __, 2000

Dear Dr. La Flore,

During FDA's preparation for the September 18-19, 2000 Dermatologic and Opthalmic Drugs Advisory Committee meeting regarding Accutane, there were discrepancies found in the numbers of reports of pregnancy exposures entered in FDA's Adverse Event Reporting System (AERS) and in your regulatory submissions. Specifically, FDA has a shortfall of approximately 1,200 reports, including reports of elective abortions or terminations of pregnancy following Accutane exposure.

Reports of all adverse reactions from both spontaneous reporting and study sources are critical to the risk management of Accutane use. To meet your postmarketing reporting requirement under 21 CFR 314.80 (c), effective the date of this letter, we request you submit the following:

1. all pregnancy exposures, regardless of the outcomes, as serious, labeled event reports in your annual periodic report;
2. a summary and discussion of the clinical significance of the pregnancy exposures in the same annual periodic report;
3. all reports of fetal abnormalities as 15-day expedited reports;
4. all reports of pregnancy exposures from whatever source, including registries, not previously submitted in official regulatory submissions (approximately 1,200 reports) as soon as possible; these reports should be submitted electronically, with clearly identified manufacturer control numbers.

We note that pregnancy exposure is not a listed outcome under the regulatory definition of "serious". Therefore, when completing 3500A forms, unless another outcome applies, we request that you check "other" under "Outcomes attributed to adverse event" and enter the term "pregnancy registry" so that the event will be captured as a serious outcome report in AERS.

If you have any questions concerning these requests or any other aspects of this letter, please contact Min Chen, Associate Director for Regulatory Affairs of the Division of Drug Risk Evaluation I, at (301) 827-3169.

Sincerely,

Peter Honig, MD, MPH
Director
Office of Postmarketing Drug Risk

Assessment

Center for Drug Evaluation and Research

Electronic Mail Message

Date: - 09 19 0000 4:06:38 PM
From: Allen Brinker
Subject: Accutane reporting

BRINKERA

Julie;

Ralph Lillie called me today to inquire about AERS support of the Accutane AC. I told him that we "learned" during our analyses of a Roche waiver - and that probably explained why we have only a fraction of the reports that Roche has.

I'm curious as to the specifics of the waiver and if there is evidence to support an investigation into compliance ?

Allen

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er,

To follow-up on this mornings meeting. Roche does, in fact, have a waiver for NDA 18-662 Accutane for non-serious labeled events. My data is located in a 11/4/99 Waiver database provided by Roger.

Best regards,

Jim Wilson P.D.
FDA, CDER, OPDRA
12300 Twinbrook Parkway
Suite 240
Rockville, MD 20851 (HFD-733)

Phone 301-770-9299 Fax 301-770-6614

Electronic Mail Message

Date: 08/31/2001 9:37:48 AM
From: Anne Trontell TRONTELLA
Subject: Answer to Julie's comments on DMD proposal

Julie and Allen,

I believe the compliance targets need to be negotiated between HLR and Derm, with input/review by CDER senior mgt. OPDRA needs to be as quantitative as possible about what various compliance targets may imply in terms of pregnancy exposures. Allen and I need to work together to bring that to closure in terms of modeling contingencies and assumptions and then writing them up.

My reason for highlighting that the goals are not yet finalized is to remind Roche that the numbers are not yet set in stone, and that their declaration of certain numbers in the context of protocols doesn't make them a matter of implicit FDA agreement. BTW, 90% tag use and 90% tag component compliance suggests a total compliance with label component of 81% just probabilistically, and that may not be acceptable to FDA.

The suggestion about having different people fill out the sticker is reasonable, but I think it complicates the issue unnecessarily. The primary point of the tag is for physicians to document PPP compliance. The Medguide (a pharmacist compliance issue) is a lesser compliance objective and one we get at least some handle from the Slone instrument. We may also be able to monitor that by other means than the pharmacist survey. I believe we will get better quality data if only one person, the MD, fills out the tag. I don't think it's that critical that the pharmacist get specialty info off the Rx. Roche could give them a list of docs and specialties based on their marketing data.

On a different metric note, I was stunned by the chart audit metric proposal that 3% of Accutane prescribers (the high volume PCPs) prescribe nearly 20% of Accutane scripts (About $36 million in sales for HLR..) That's more than any dermatologic category. These high volume PCPs sound like they could be "acne mills" and so may deserve highly targeted educational and compliance checks

BTW, in my opinion the chart audit metric is unacceptable for ethical as well as scientific validity reasons. We should get that message to Roche early next week after we discuss internally.

Anne

>Anne,
>
>This is very nice. I had a couple of comments:
>
>1) What do you have in mind regarding compliance targets? Do you think they should/could be higher?
>
>2) With regard to your questions 3 & 16 about who would be answering
>which questions on the QT (e.g., re: Medication Guides), I'd suggest

Electronic Mail Message

Date: 8/16/01 2:44:40 PM
From: O Connell, Kathryn A [redacted]
To: See Below
Subject: Re: follow-up on third metric from yesterday meeting...

Hi Allen

I think teratogen-exposed pregnancies probably stick in the memory of abortion providers for exactly the fact you point out: they are a very sad anomaly amongst the background of much more pedestrian reasons for seeking help.

As for the "needle", I think you and a lot of other non-dermatologists are in for a major shock IF the truth is ever exposed. I know what I am going to say is anecdote, but I personally know several derms whose patients have become pregnant on Accutane and NOT A SINGLE one reported it (except to their lawyer). And I don't even know that many derms, as I am not into the local derm scene!!

On top of this, as you pointed out yesterday, a patient got pregnant in the new formulation trial despite the small number of women enrolled (a good number of whom were probably not even sexually active given ages), the incredible scrutiny of a very tight clinical trial protocol, an investigator who happened to be president of the AAD and chair of the DODAC, and a father who discussed risk with her AND is professor of gynecology. Personally, I do not find this reassuring about anything, much less the "representativeness" of the Slone!

Roche and the AAD are so adamantly opposed to collecting the real number of exposed fetuses for a reason and I personally do not believe them when they say it is concern for patients' privacy (we do NOT have to compromise that in any way to collect the data). I think it is concern about the public outcry/outrage that will ensue if the truth comes out.

The 2 reasons patients give for NOT participating in Slone are: 1) too much trouble (so is rigid adherence to contraceptive measures) and 2) their doctor did not tell them to (likely the same doctors who don't tell them a lot of other important messages about avoiding fetal exposure). I think we are all deluding ourselves to think that the current Slone survey is representative of anything except the very best-case scenario and patients in it STILL get pregnant on Accutane!

I hope I am terribly wrong about this, but if we are looking for a "needle in a haystack", it is a VERY VERY large fluorescent knitting needle that should stand out quite adequately in all this darkness.

-----Original Message-----
From: Allen Brinker 301-827-3163 FAX 301-827-5190
To: O Connell, Kathryn A; Bull, Jonca; Trontell, Anne E; Beitz, Julie G; Pitts, Marilyn; Furlong, Leslie Ann
Cc: Wilkin, Jonathan K; Kozma-Fornaro, Mary J
Sent: 8/16/01 1:46 PM
Subject: Re: follow-up on third metric from yesterday meeting...
Sensitivity: Confidential

Kathy;

I agree with your assessment of the third metric proposed by HLR