FDA Pregnancy and Lactation Labeling Rule

Considerations for Populating Lactation Section 8.2

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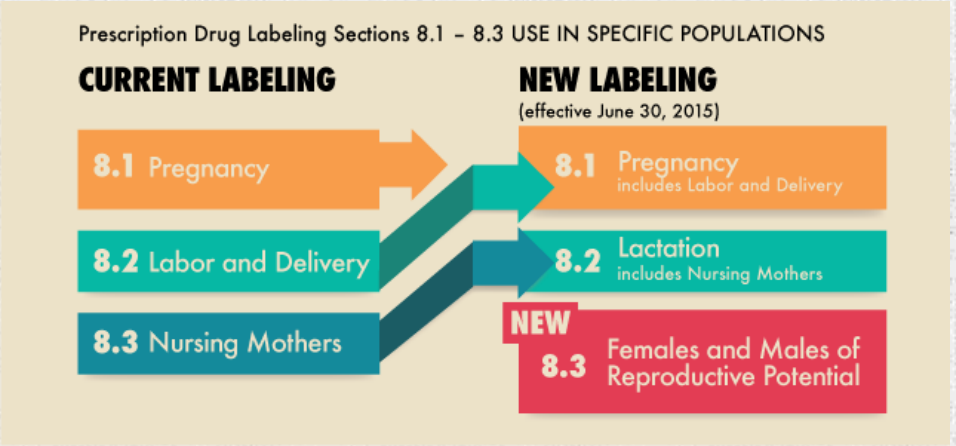
To Absent Friends:
the Missing Medications we Wish Were Here.

Drug Labeling & Lactation

FDA Pregnancy and Lactation Labeling Rule (PLLR)



- Rx drugs/biologics submitted after 6/30/15 will use the new format.
- Those approved on/after 6/30/01 will be phased in gradually (3 yrs).

Who is absent?

- Drugs with data in the literature but not in the label
- Drugs with no/sparse data in the literature and not in label
- Label content in some drugs that have adopted new format

Target Drugs

- Commonly/likely used by women of reproductive age
  - Antimicrobials
  - Anti-inflammatory/Immunotherapy
  - Cardiovascular
  - Hormones/Endocrine
  - Neuro/Psych
- Health risk for the exposed infant
  - Not infant/pediatric approved or therapeutically used
  - In a class of agents each with varying degrees of risk
  - Potential side effects uniquely harmful in infants
- Not a known health risk for the exposed infant
- Those with approved commercial/research assays
  - To test milk (once developed) and/or infant serum/urine

Target Drugs - Antimicrobials

	Risk < Benefit	Risk ? > Benefit
Data	Azithromycin Ceftazidime Ciprofloxacin Ertapenem Linezolid Meropenem*	Doxycycline
No data	Benzyl alcohol Cefditoren Ceftaroline Doripenem Tedizolid	Daptomycin Gemifloxacin Levofloxacin Moxifloxacin Posaconazole Tigecycline Voriconazole

- Low priority: Inhaled tobramycin, echinocandins
- Pre 6/30/01: ceftriaxone, flucon, fosfomycin, vanco, TB
- Study design considerations: stool flora diversity

*weak data

Target Drugs – Anti-inflammatory

	Risk < Benefit	Risk ? > Benefit
Data	IFN β-1a Ibuprofen Diclofenac* Prednisone*	Ertanacept mABs Naproxen*
No data	Anakinra Glatiramer Dimethyl fumarate Esomeprazole Meloxicam	Fusion proteins mABs Fingolimod Teriflunomide Tofacitinib

- Low priority: medications for gout
- Pre 6/30/01: MMF, MTX, inj corticosteroids
- Study design considerations: regional GI mAB effects, health status outcomes with biological DMARDs.

*weak data

Target Drugs - Cardiovascular

	Risk < Benefit	Risk ? > Benefit
Data	Amlodipine Dalteparin Enoxaparin HCTZ*	Rosuvastatin* Metoprolol
No data	Desirudin Evolocumab Mipomersen Omega 3 FA	AARBs, ACEIs Aliskiren Ezetimibe anti-Factor Xa HMG CoA Lomitapide

- Low priority: bivalirudin, peri-PCI, ivabradine, PHTN, vorapaxar
- Pre 6/30/2001: Felodipine, furosemide, lisinopril

*weak data

Target Drugs - Endocrine

	Risk < Benefit	Risk ? > Benefit
Data	Insulin Glipizide, Glyburide Metformin Drospirenone Levonorgestrel Norethindrone T4*	Ethinyl estradiol
No data	Etonogestrel ring Norelgestromin patch	Estradiol valerate/ dienogest

- Low priority: -gliptins, -flozins, -tides, wt loss, pancrealipase

*weak data

Target Drugs – Neuro/Psychiatry

	Risk < Benefit	Risk ? > Benefit
Data	Gabapentin Eslicarbazepine Lacosamide* Sumatriptan Topiramate Vigabatrin* Tramadol	Clonidine Clobazam* Fentanyl patch* Hydrocodone ER* Hydromorphone ER* Morphine ER* Oxycodone ER*
No data	Brivaracetam Rufinamide Vilazodone	Dalfampridine Guanfacine Levomilnacipran Perampanel

- Low priority – eszopiclone, suvorexant, zolpidem

*weak data

Current PLLR-Compliant Examples

Lesinurad (Zurampic) Dec 2015

8.2 Lactation

Risk Summary. There is no information regarding the presence of ZURAMPIC in human milk, the effects on the breastfed infant, or the effects on milk production. Lesinurad is present in the milk of rats. *[Standard statement]**

*The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZURAMPIC and any potential adverse effects on the breastfed infant from ZURAMPIC or from the underlying maternal condition.

Current PLLR-Compliant Examples

Lesinurad (Zurampic) April 27, 2016

8.2 Lactation

Risk Summary. The risks of ZURAMPIC during breastfeeding have not been directly studied. ZURAMPIC is highly protein bound and has a relatively short half-life (*see Pharmacokinetics 12.3*). The predicted risk of clinically significant exposure of the breastfed infant through breastmilk is therefore low. *[Standard statement]*

Clinical. Because ZURAMPIC is given once daily, minimizing daily exposure to the breastfed infant can be accomplished by avoiding breastfeeding 2-4 hours after a dose. Infants breastfed by mothers using ZURAMPIC should have serum creatinine and urinary uric acid concentrations monitored periodically

Data. There are no data describing the transfer of ZURAMPIC to human milk. Although ZURAMPIC is present in the milk of rats, animal data poorly predict human milk transfer.

Current PLLR-Compliant Examples

Cholic acid (Cholbam) March 2015

8.2 Lactation

Risk Summary

Endogenous cholic acid is present in human milk. Clinical lactation studies have not been conducted to assess the presence of CHOLBAM in human milk, the effects of CHOLBAM on the breastfed infant, or the effects of CHOLBAM on milk production. There are no animal lactation data and no data from case reports available in the published literature. *[Standard Statement]*

New label better than the old?

8.3 Nursing Mothers

It is not known whether CHOLBAM passes into breast milk. Therefore, CHOLBAM should not be taken during lactation. If treatment with CHOLBAM is necessary, the infant should be weaned.

OLD

NEW

Current PLLR-Compliant Examples

Cholic acid (Cholbam) April 27, 2016

8.2 Lactation

Risk Summary

Cholic acid is normally present in the bile acid pool of healthy mothers and infants.

Mothers who take CHOLBAM for bile acid synthesis or peroxisomal disorders are not expected to have higher cholic acid pools, serum concentrations, or breastmilk concentrations than normal healthy mothers.

Other chemically similar, medicinal, natural bile acids such as ursodeoxycholic acid (UDCA), are known to transfer to breastmilk in insignificant amounts in mothers who take UDCA.

[Standard Statement]

Current PLLR-Compliant Examples

Cholic acid (Cholbam) April 27, 2016

8.2 Lactation

Clinical Considerations

Monitor breastmilk fed infants for changes in stool habits and for the occurrence of diaper dermatitis.

Data

There are no data describing the transfer of CHOLBAM to human milk.

The concentration of cholic acid in the colostrum of healthy mothers is approximately 0.2 mcg/L. A breastfed infant normally consumes 30-40 mcg/kg/day of cholic acid.

Current PLLR-Compliant Examples

Buprenorphine (Belbuca) October 2015

8.2 Lactation

Risk Summary

Based on two studies in 13 lactating women being treated for opioid dependence and their breastfed infants, buprenorphine and its metabolite norbuprenorphine are present in low levels in human milk and infant urine, and available data have not shown adverse reactions in breastfed infants [see Data]. There are no data on the effects of BELBUCA on milk production. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with BELBUCA.

Clinical Considerations Infants exposed to BELBUCA through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of buprenorphine is stopped or when breast-feeding is stopped.

Current PLLR-Compliant Examples

8.2 Lactation Risk Summary

Data

Based on limited data from a study of six lactating women being treated for opioid dependence who were taking a median oral dose of buprenorphine of 0.29 mg/kg/day 5-8 days after delivery, breast milk contained a median infant dose of 0.42 mcg/kg/day of buprenorphine and 0.33 mcg/kg/day of norbuprenorphine, which are equal to 0.2% and 0.12% of the maternal weight-adjusted dose. The median concentrations of buprenorphine and norbuprenorphine in infant urine were 1.0 nmol/L and 2.3 nmol/L, respectively.

Based on limited data from a study of seven lactating women being treated for opioid dependence who were taking a median oral dose of buprenorphine of 7 mg/day an average of 1.12 months after delivery, the mean milk concentrations of buprenorphine and norbuprenorphine were 3.65 mcg/L and 1.94 mcg/L, respectively. Based on the limited data from this study, and assuming milk consumption of 150 mL/kg/day, an exclusively breastfed infant would receive an estimated mean of 0.55 mcg/kg/day of buprenorphine and 0.29 mcg/kg/day of norbuprenorphine, which are 0.38% and 0.18% of the maternal weight-adjusted dose. No adverse reactions were observed in the infants in these two studies.

Current PLLR-Compliant Examples

Pregabalin (Lyrica) March 2016

8.2 Lactation

Risk Summary

Small amounts of pregabalin have been detected in the milk of lactating women. A pharmacokinetic study in lactating women detected pregabalin in breast milk at average steady state concentrations approximately 76% of those in maternal plasma. The estimated average daily infant dose of pregabalin from breast milk (assuming mean milk consumption of 150 mL/kg/day) was 0.31 mg/kg/day, which on a mg/kg basis would be approximately 7% of the maternal dose [see Data]. The study did not evaluate the effects of LYRICA on milk production or the effects of LYRICA on the breastfed infant.

Current PLLR-Compliant Examples

Pregabalin (Lyrica) March 2016

8.2 Lactation

Based on animal studies, there is a potential risk of tumorigenicity with pregabalin exposure via breast milk to the breastfed infant [see Nonclinical Toxicology (13.1)]. Available clinical study data in patients greater than 12 years of age do not provide a clear conclusion about the potential risk of tumorigenicity with pregabalin [see Warnings and Precautions (5.9)]. Because of the potential risk of tumorigenicity, breastfeeding is not recommended during treatment with LYRICA.

Data

A pharmacokinetic study in ten lactating women, who were at least 12 weeks postpartum, evaluated the concentrations of pregabalin in plasma and breast milk. LYRICA 150 mg oral capsule was given every 12 hours (300 mg daily dose) for a total of four doses. Pregabalin was detected in breast milk at average steady-state concentrations approximately 76% of those in maternal plasma. The estimated average daily infant dose of pregabalin from breast milk (assuming mean milk consumption of 150 mL/kg/day) . . . . .

Current PLLR-Compliant Examples

Leflunomide (Arava) August 2015

8.2 Lactation

Risk Summary

Clinical lactation studies have not been conducted to assess the presence of ARAVA in human milk, the effects of ARAVA on the breastfed child, or the effects of ARAVA on milk production. Because of the potential for serious adverse reactions in a breastfed infant from ARAVA, advise a nursing woman to discontinue breastfeeding during treatment with ARAVA.

Current PLLR-Compliant Examples

Indomethacin (Tyvorbex) February 2014

8.3 Nursing Mothers

Based on available published data, indomethacin may be present in human milk. In one study, levels of indomethacin in breast milk were below the sensitivity of the assay (<20 mcg/L) in 11 of 15 women using doses ranging from 75 mg orally to 300 mg rectally daily (0.94 to 4.29 mg/kg daily) in the postpartum period. Based on these levels, the average concentration present in breast milk was estimated to be 0.27% of the maternal weight-adjusted dose. In another study indomethacin levels were measured in breast milk of eight postpartum women using doses of 75 mg daily and the results were used to calculate an estimated infant daily dose. The estimated infant dose of indomethacin from breast milk was less than 30 mcg/day or 4.5 mcg/ kg/day assuming breast milk intake of 150 ml/kg/day. This is 0.5% of the maternal weight-adjusted dosage or about 3% of the neonatal dose for treatment of patent ductus arteriosus. The developmental and health benefits of human milk feeding should be considered along with the mother's clinical need for TIVORBEX and any potential adverse effects on the human milk-fed child from the drug or from the underlying maternal condition. Exercise caution when TIVORBEX is administered to a nursing woman.

Conclusions

- An estimated 50% of drugs due for PLLR conversion have data already in the literature.
- Labels for drugs with no data should utilize PK and clinical pragmatism to define risk.
- A consistent approach to label content and format will improve usability.
- Drugs with presumed low risk and no data should be a research priority.

Thank you

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