

# Communicating HTE to Key Stakeholders

Catherine Y Spong MD  
UT Southwestern Medical Center

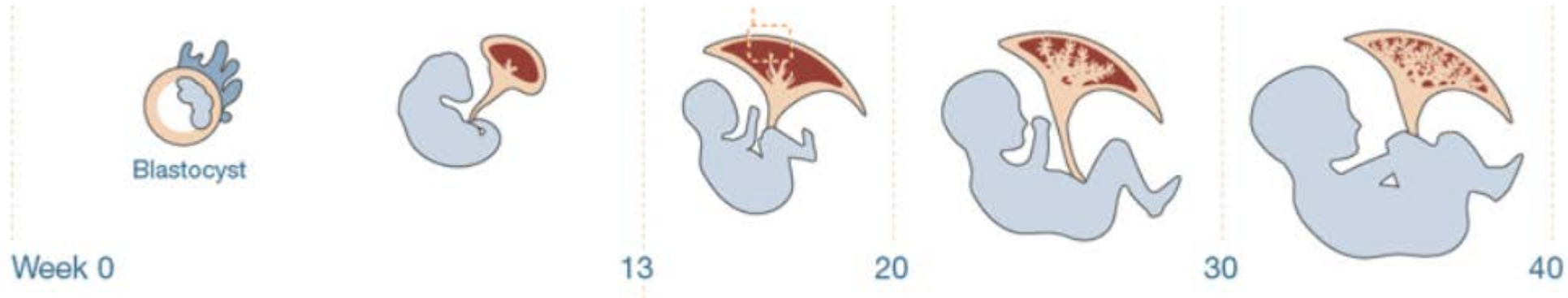
What are the main issues surrounding heterogeneity of treatments effects\* in pregnant and lactating women, and how do current communication avenues (ex. drug labelling) serve clinical decision making for both providers and patients?



*\*Some patients will experience more or less benefit from treatment than the averages reported from clinical trials; such variation in therapeutic outcome is termed heterogeneity of treatment effects (HTE). Identifying HTE is necessary to individualize treatment.*

# HTE in pregnant and lactating women

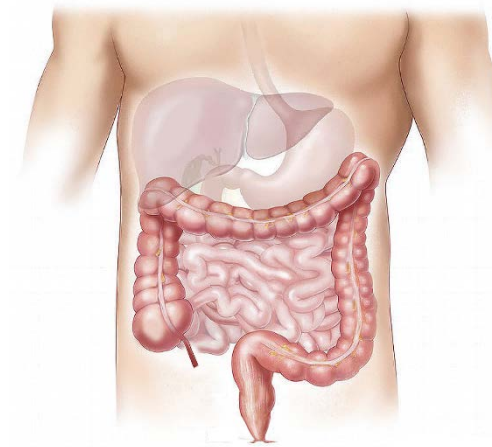
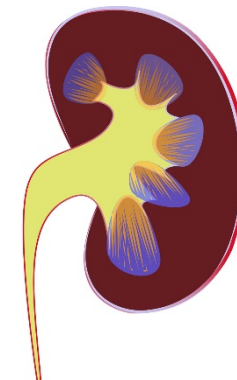
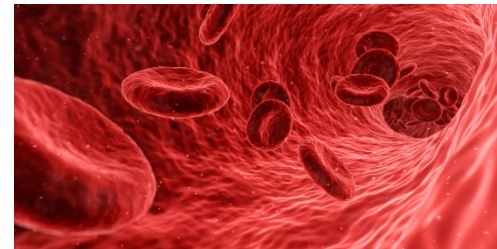
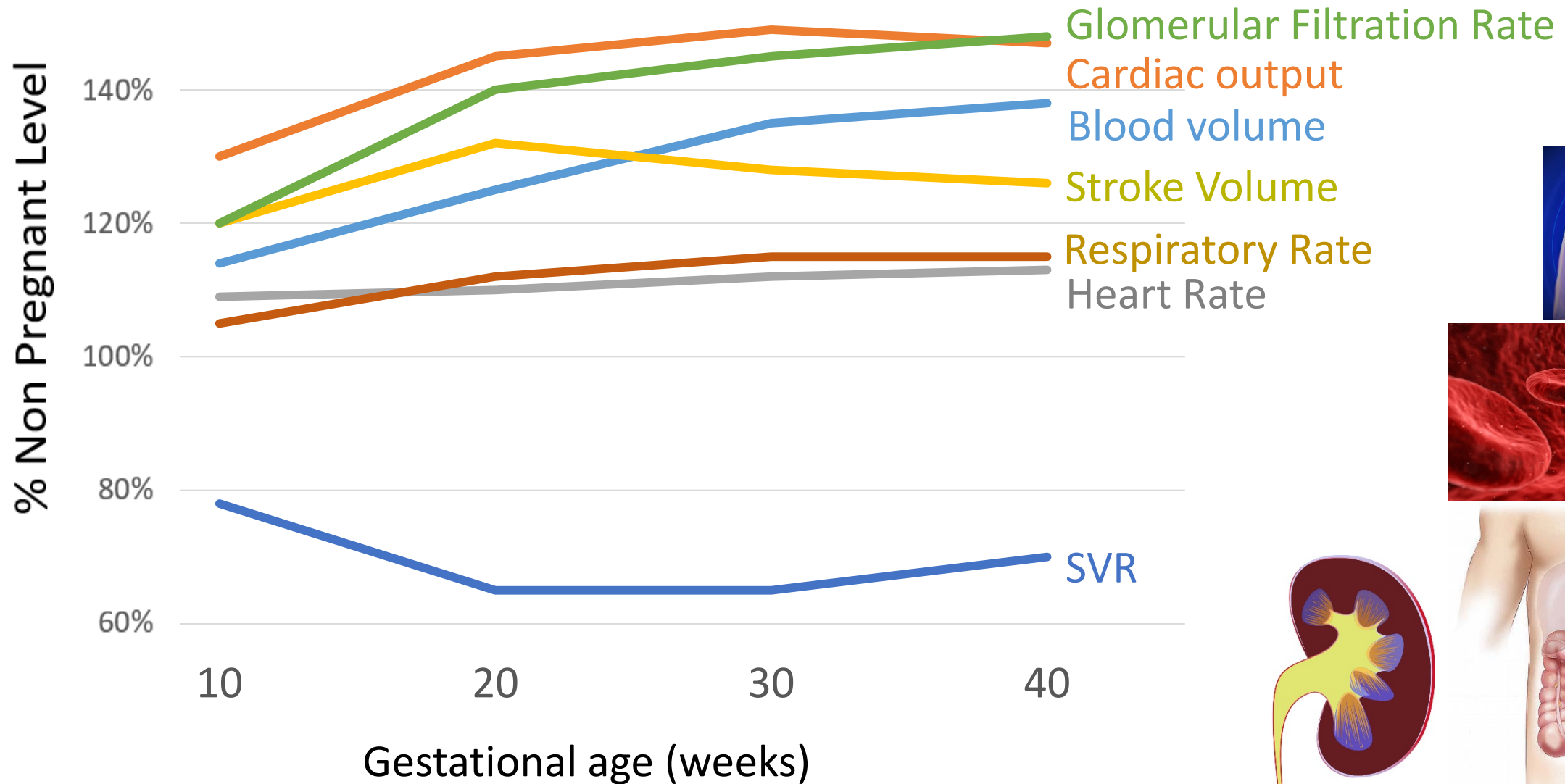
- Physiologic changes across gestation and lactation
  - HTE within as well as across the subpopulations
- Lack of available information
- Limited ongoing research
- Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)
- Communication avenues: Drug Labelling



Physiologic changes



# Physiologic changes across gestation



# Physiologic changes across lactation

- Composition of human breast milk changes
- During each nursing, the initial milk (foremilk) is thinner with a higher content of lactose
- The latter milk (hindmilk) is creamier with a higher content of fat
- Other changes
  - age of the infant
  - maternal diet
  - maternal health
  - environmental exposure



# Limited data available

*Pregnancy and Lactation Publications on Medicinal Therapies for Asthma, by Publication Type, 2006-2017*

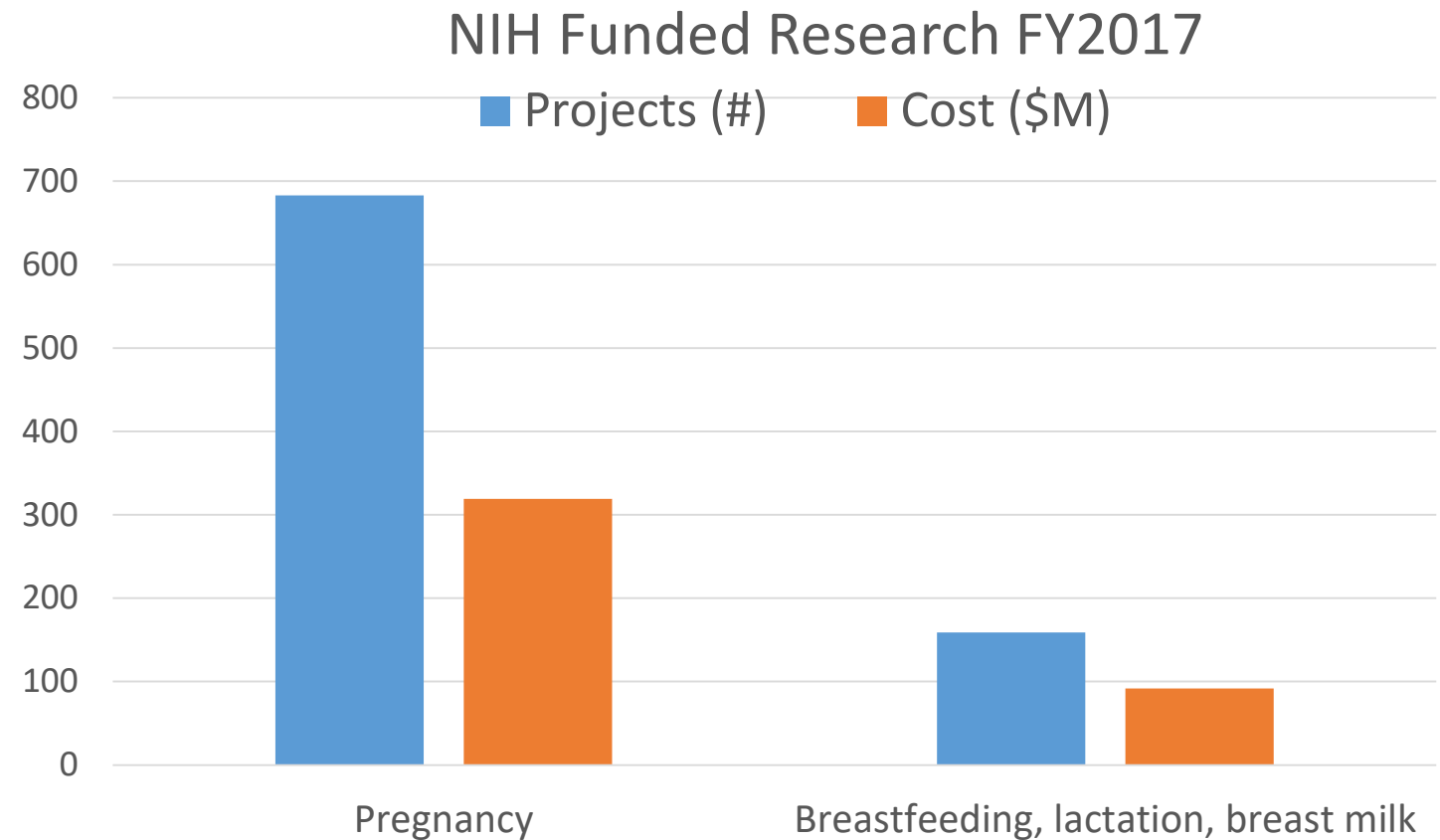
Condition	Basic	PK/PD	Pop/DB	RCT	Case series	Case Reports	Reviews	Editorial/Comment	Other
Asthma (Pregnancy)	21	0	60	4	58	29	184	29	26
Asthma (Lactation)	3	0	0	0	1	1	11	0	0

Almost all the pregnancy- and lactation-related research focused on pregnancy only, and not lactation.

\*Of note, prevalence of asthma in pregnant women is ~8.5%; with 4% of pregnant women experiencing an asthma attack in the prior year

# NIH Funding Research on Pregnancy, Breastfeeding, lactation and breast milk

- Pregnancy
  - 683 projects, \$319 M total
  - 21 ICs + NIH OD
  - 1% of NIH extramural funding
- Breastfeeding, Lactation, and Breast Milk
  - 159 projects, \$91.7 M total
  - 20 ICs + NIH OD
  - 0.3% NIH extramural funding



NIH extramural budget 2017: ~30 B (<https://report.nih.gov/NIHDatabook/Charts/Default.aspx?showm=Y&chartId=283&catId=1>)

PRGLAC report ([https://www.nichd.nih.gov/sites/default/files/2018-09/PRGLAC\\_Report.pdf](https://www.nichd.nih.gov/sites/default/files/2018-09/PRGLAC_Report.pdf))

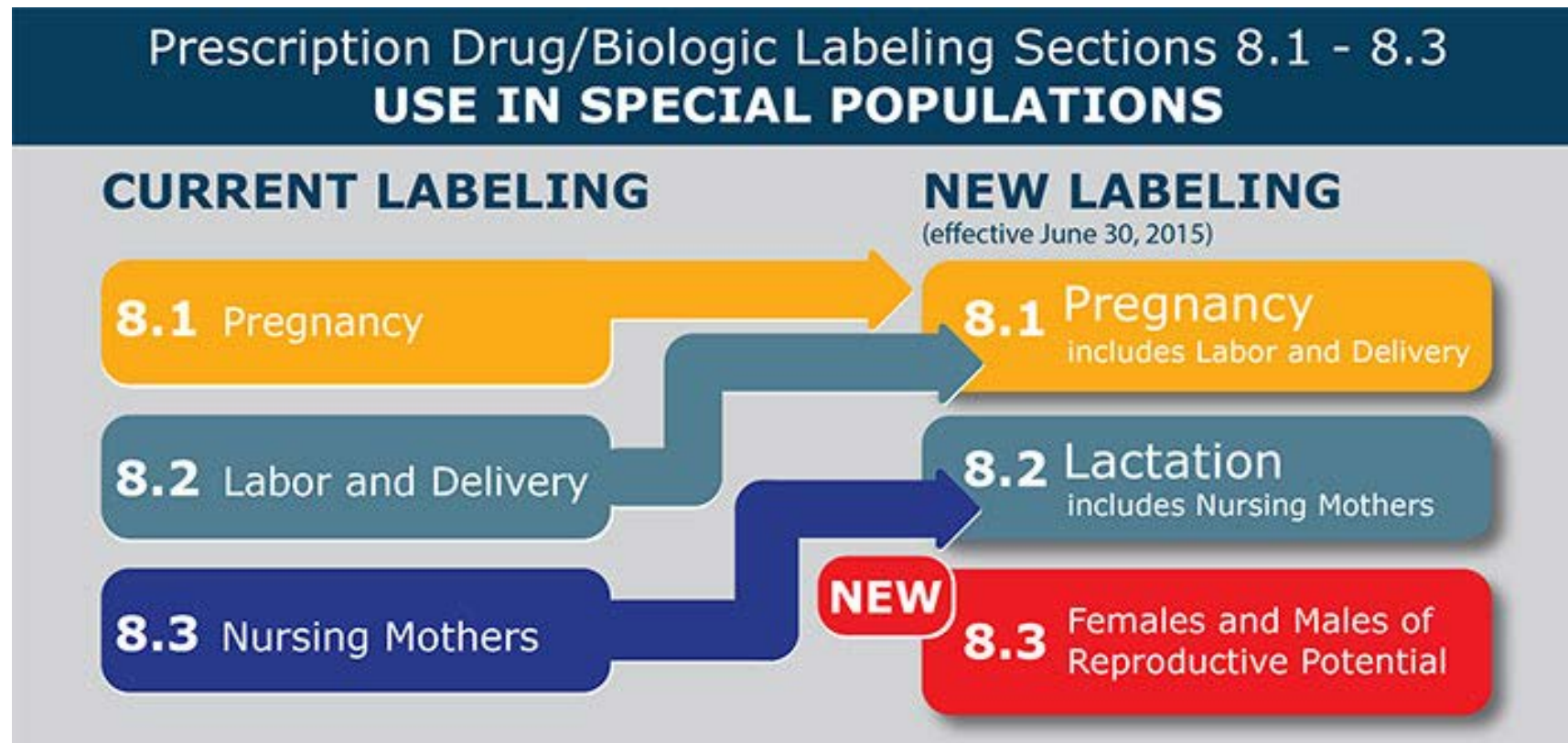
# Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)

- In the US, >6 million women become pregnant, 4M deliver, 3M breastfeed and 30% are breastfeeding at a year
- >90% of women take medications in pregnancy; 70% are prescribed medications in pregnancy
- PRGLAC established by 21<sup>st</sup> Century Cures Act to develop a report including a plan and recommendations for safe and effective therapies for pregnant and lactating women
- Report delivered 9/2018; HHS Secretary to act by December 2018



# Communication

- Drug Label
- PLLR modifications



## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

Based on animal studies and its mechanism of action, ZYKADIA can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology (12.1)*]. The limited available data on the use of ZYKADIA in pregnant women are insufficient to inform a risk. Administration of ceritinib to rats and rabbits during the period of organogenesis at maternal plasma exposures below the recommended human dose caused increases in skeletal anomalies in rats and rabbits [see *Data*]. Advise a pregnant woman of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively.

#### Data

##### Animal Data

In an embryo-fetal development study in which pregnant rats were administered daily doses of ceritinib during organogenesis, dose-related skeletal anomalies were observed at doses as low as 50 mg/kg (less than 0.5-fold the human exposure by AUC at the recommended dose). Findings included delayed ossifications and skeletal variations.

In pregnant rabbits administered ceritinib daily during organogenesis, dose-related skeletal anomalies, including incomplete ossification, were observed at doses equal to or greater than 2 mg/kg/day (approximately 0.015-fold the human exposure by AUC at the recommended dose). A low incidence of visceral anomalies, including absent or malpositioned gallbladder and retroesophageal subclavian cardiac artery, was observed at doses equal to or greater than 10 mg/kg/day (approximately 0.13-fold the human exposure by AUC at the recommended dose). Maternal toxicity and abortion occurred in rabbits at doses of 35 mg/kg or greater. In addition, embryoletality was observed in rabbits at a dose of 50 mg/kg.

## **8.2 Lactation**

### Risk Summary

There are no data regarding the presence of ceritinib or its metabolites in human milk, the effects of ceritinib on the breastfed infant, or its effects on milk production. Because of the potential for serious adverse reactions including gastrointestinal adverse reactions, hepatotoxicity, pneumonitis, bradycardia and pancreatitis, advise a woman not to breastfeed during treatment with ZYKADIA and for 2 weeks following completion of therapy.

## **8.3 Females and Males of Reproductive Potential**

### Contraception

#### Females

ZYKADIA can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment with ZYKADIA and for 6 months following completion of therapy.

#### Males

Based on the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with ZYKADIA and for 3 months following completion of therapy [*see Nonclinical Toxicology (13.1)*].

# Pregnancy Registries

Communicating with Health Care Providers and Consumers



[www.fda.gov/pregnancyregistries](https://www.fda.gov/pregnancyregistries)

- Connect Pregnant women and health professionals to over 40 registries
- Links to drug information
- Patient education resources
- New web buttons