Pregnancy Outcomes With Teriflunomide: Female Patients and Partners of Male Patients

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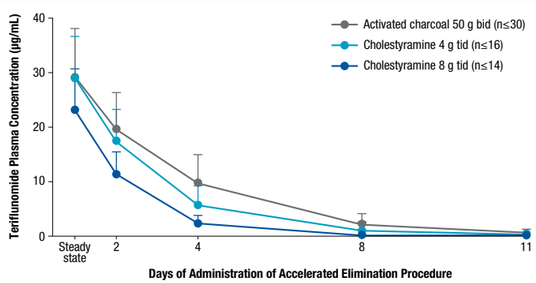
BACKGROUND

- Teriflunomide is a once-daily, oral disease-modifying therapy approved for the treatment of patients with relapsing forms of multiple sclerosis (MS).[1]
  - Exposure across more than 10 years of the teriflunomide clinical program exceeds 3700 patient-years.
- Preclinical evidence regarding embryofetal toxicity demonstrates that teriflunomide:[1]
  - is non-mutagenic in vitro
  - does not affect chromosomes (mice, rats, hamsters) or fertility (rats)
  - has teratogenic effects in rats and rabbits.
- Teriflunomide is the principal active metabolite of leflunomide, used in the treatment of rheumatoid arthritis (RA) since 1998.[2]
  - Embryo-lethality and teratogenicity were observed in leflunomide animal studies.
  - In the prospective Organization of Teratology Information Services (OTIS) study, patients with RA were exposed to leflunomide in the first trimester of pregnancy and underwent accelerated elimination.[3]
  - No significant differences were observed in the overall rate of major structural defects compared with disease-matched and healthy controls, there was no evidence of teratogenicity, and the rate of spontaneous abortion was similar to that in the general population.[3,4]
- Based on animal studies, women of childbearing potential must use reliable contraception when receiving teriflunomide.[1]
- Teriflunomide has been detected in human semen; animal studies to evaluate risk of male-mediated fetal toxicity have not been conducted. In humans, the estimated female exposure via semen of a male treated patient is expected to be 100 times lower than the steady-state plasma exposure with 14 mg oral dosing. However, to minimize any possible risk, patients receiving teriflunomide should use reliable contraception.[1]
- If pregnancy is desired, patients—female or male—must discontinue treatment and undergo an elimination procedure with cholestyramine or activated charcoal until teriflunomide plasma concentrations are <0.02 µg/mL (**Figure**).

Figure. Plasma Elimination of Teriflunomide Using Accelerated Elimination Procedure



Teriflunomide elimination can be accelerated by either of the following procedures:

- Administration of cholestyramine 8 g three times daily (tid) for 11 days. If cholestyramine 8 g tid is not well tolerated, cholestyramine 4 g tid can be used.
- Administration of 50 g oral activated charcoal powder twice daily (bid) for 11 days.

OBJECTIVE

- Summarize pregnancy outcomes in female patients and partners of males exposed to teriflunomide across 9 phase 2/3 clinical studies in the MS clinical development program.

METHODS

- Patients received teriflunomide (7 or 14 mg), interferon-β, placebo, or a combination of treatments in 9 different clinical studies (**Table 1**).
- Although reliable contraception was required during the studies for women of childbearing potential and men with partners of childbearing potential, a number of pregnancies were reported.

Table 1. Teriflunomide Clinical Development Program

Study / Phase	Treatment Arms	Treatment Duration	Randomized†
Monotherapy Studies			
Phase 2* / 2	Placebo, 7 mg, 14 mg teriflunomide	36 weeks	179 (Females: Placebo 41, 7 mg teriflunomide 46, 14 mg teriflunomide 45)
TERIVA / 2	IFN β, 7 mg, 14 mg teriflunomide	28 days, vaccination on Day 1	128 (Females: IFN β 32, 7 mg teriflunomide 28, 14 mg teriflunomide 29)
TEMSO* / 3	Placebo, 7 mg, 14 mg teriflunomide	108 weeks	1088 (Females: Placebo 275, 7 mg teriflunomide 255, 14 mg teriflunomide 255)
TOWER* / 3	Placebo, 7 mg, 14 mg teriflunomide	Range 48–152 weeks (mean 78 weeks)	1169 (Females: Placebo 273, 7 mg teriflunomide 300, 14 mg teriflunomide 258)
TENERE* / 3	IFN β-1a, 7 mg, 14 mg teriflunomide	Range 48–118 weeks (median 64 weeks)	324 (Females: IFN β 71, 7 mg teriflunomide 70, 14 mg teriflunomide 78)
TOPIC* / 3	Placebo, 7 mg, 14 mg teriflunomide	108 weeks	618 (Females: Placebo 135, 7 mg teriflunomide 130, 14 mg teriflunomide 154)
Adjunctive Therapy Studies			
Teri + GA* / 2	GA + Placebo or 7 mg, 14 mg teriflunomide	24 weeks	123 (Females: GA 32, 7 mg teriflunomide 33, 14 mg teriflunomide 32)
Teri + IFN β* / 2	IFN β + Placebo or 7 mg, 14 mg teriflunomide	24 weeks	118 (Females: IFN β + placebo 31, IFN β + 7 mg teriflunomide 25, IFN β + 14 mg teriflunomide 25)
TERACLES / 3	IFN β + Placebo or 7 mg, 14 mg teriflunomide	Variable	534

GA, glatiramer acetate; IFN β, interferon beta. *Study designs included optional extension. †Not all females were of childbearing potential.

- Information (where available) was collected using a Drug Exposure Via Parent form including treatment allocation, pregnancy outcome, patient and fetal exposure, and accelerated elimination procedure.
- The data cut-off was April 9, 2013.

RESULTS

Pregnancies in Female Patients

- Eighty-one pregnancies were reported in female patients across the studies.
  - 63 pregnancies occurred in patients exposed to teriflunomide.
  - 18 pregnancies occurred in patients treated with placebo or interferon-β, or who remained blinded with respect to treatment group; 1 pregnancy was identified at screening.
- Outcomes of the pregnancies are reported in **Table 2**. Of the 25 live births, 20 were born to patients exposed to teriflunomide.

Table 2. Pregnancy Outcomes in Female Patients

	Pregnancy Outcome, n			
Treatment	Live Birth	Induced Abortion	Spontaneous Abortion	Ongoing Pregnancy
Teriflunomide	20	26	12	5
Placebo	2	6	1	0
Interferon-β	2	0	0	0
Blinded therapy	1	3	1	2

- All 20 teriflunomide-treated women giving birth to live infants had already discontinued teriflunomide or discontinued a few days to 11 weeks after becoming pregnant.
  - All patients underwent an accelerated elimination procedure after discontinuing treatment except 2 patients who refused.
  - 7 became pregnant after completing the accelerated elimination procedure.
- All 20 newborns were healthy, without structural or functional problems.
  - Mean known birth weight was 3415 g (range 2780–4150 g) for 12 newborns.
  - Mean gestational age was 38 weeks (range 37–41 weeks).
  - No malformations were reported.
- The rate of spontaneous abortion in the teriflunomide group (19.0%) was within the range reported for the non-MS population.[5]

Pregnancies in Partners of Male Patients

- Twenty pregnancies were reported in partners of 17 men in teriflunomide clinical trials.
  - In 16 pregnancies, the father had been exposed to teriflunomide; in 1 case, the patient remained blinded with respect to treatment group.
- Pregnancy outcomes are reported in **Table 3**.

Table 3. Pregnancy Outcomes in Partners of Male Patients

	Pregnancy Outcome, n			
Treatment	Live Birth	Induced Abortion	Spontaneous Abortion	Ongoing Pregnancy
Teriflunomide	12	1	1	2
Placebo	3	0	0	0
Blinded therapy	0	1	0	0

- All newborns were healthy and free from structural and functional abnormalities.
- There was 1 spontaneous abortion reported in a partner of a man receiving teriflunomide.

CONCLUSIONS

- Teriflunomide clinical data to date have not shown a teratogenic signal, consistent with the findings of the leflunomide OTIS registry.
  - Pregnancy outcomes among women who received teriflunomide, including rates of spontaneous abortion, and gestational age and weight at birth, are consistent with those for the non-MS population.
  - Babies born to mothers or fathers who received teriflunomide had no structural or functional abnormalities at birth.
- Teriflunomide is a therapeutic option for women of childbearing potential, and for male patients with female partners of childbearing potential, when using reliable contraception.
  - If a woman receiving teriflunomide becomes or wishes to become pregnant, she should undergo an accelerated elimination procedure and verify teriflunomide plasma concentrations to be <0.02 µg/mL.
  - If a man receiving teriflunomide has a pregnant partner, he should discontinue treatment and undergo accelerated elimination.
- Planned teriflunomide pregnancy registries will provide additional information.

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