

TERIS Summary

TERIS Agent Number: 6357 Bibliographic Search Date: 12/2022
Agent Name: **TOCILIZUMAB**

Tocilizumab is a humanized anti-interleukin-6 receptor monoclonal antibody that is administered intravenously in the treatment of inflammatory autoimmune diseases. The elimination half-life is approximately ten days.

Magnitude of Teratogenic Risk to Child Born After Exposure During Gestation: UNDETERMINED

Quality and Quantity of Data on Which Risk Estimate is Based: LIMITED

Comments: 1) A SMALL RISK CANNOT BE EXCLUDED, BUT A HIGH RISK OF CONGENITAL ANOMALIES IN THE CHILDREN OF WOMEN TREATED WITH THERAPUTIC DOSES OF TOCILIZUMAB DURING PREGNANCY IS UNLIKELY.
2) BECAUSE TOCILIZUMAB IS AN ANTIBODY, IT MAY BE ACTIVELY TRANSPORTED ACROSS THE PLACENTA IN LATER PREGNANCY.

Summary of Teratology Studies:

MAJOR CONGENITAL ANOMALIES

The frequency of major malformations was not significantly increased among the infants of 124 women treated with tocilizumab during pregnancy compared to the infants of 1179 women who were exposed in pregnancy to certolizumab pegol, a presumably safe biologic, in a retrospective cohort study using the EudraVigilance database (adjusted odds ratio=0.79, 95% confidence interval 0.37-1.68) (Ghalandari et al., 2022).

In the largest case-series published from the manufacturer's safety database, congenital anomalies were observed in five (4.5%, 95% confidence interval 1.5-10.2%) of 111 liveborn infants whose mothers were treated with tocilizumab during the first trimester of pregnancy and prospectively reported to the manufacturer (Hoeltzenbein et al., 2016). No recurrent pattern of birth defects was observed among these infants. No congenital anomalies were reported in any of the 33 spontaneous abortions or 31 electively terminated pregnancies that were prospectively reported to the manufacturer. Different malformations have been reported retrospectively among fetuses or infants whose mothers had taken tocilizumab early in pregnancy (Hoeltzenbein et al., 2016; Nakajima et al., 2016; Weber-Schoendorfer & Schaefer, 2016). No recurrent pattern of anomalies was apparent in these four anecdotal reports.

ADVERSE PREGNANCY AND NEONATAL OUTCOMES

Data on fetal effects following maternal use of tocilizumab in later pregnancy for the indication of COVID -19 have been reported in a total of 19 pregnancies (San-Juan et al., 2020; Abdullah et al., 2021; Jimenez-Lozano et al., 2021). Many of these mothers were critically ill and were treated concomitantly with other medications. Four of the infants were delivered prematurely. A patient with an adult-onset Still's disease, who exhibited hyperthermia, arthritis, and liver dysfunction, was treated with tocilizumab in the second half of pregnancy and delivered a healthy term-infant (Imaizumi et al., 2022).

ANIMAL TERATOLOGY STUDIES

Animal teratology studies of tocilizumab performed by the manufacturer have not been published in the peer-reviewed literature.

Selected References:

(Each paper is classified as a review [R], human case report [C], human epidemiological study [E], human clinical series [S], animal study [A], or other [O].)

Abdullah S, Bashir N, Mahmood N: Use of intravenous tocilizumab in pregnancy for severe coronavirus disease 2019 pneumonia: two case reports. J Med Case Rep 15(1):426, 2021. [C]

Ghalandari N, Crijns HJM, Bergman JEH, Dolhain RJEM, van Puijenbroek EP, Hazes JMW: Reported congenital malformations after exposure to non-tumour necrosis factor inhibitor biologics: a retrospective comparative study in EudraVigilance. Br J Clin Pharmacol 88(12):5378-5388, 2022. [E]

Hoeltzenbein M, Beck E, Rajwanshi R, Gotestam Skorpen C, Berber E, Schaefer C, Ostensen M: Tocilizumab use in pregnancy: analysis of a global safety database including data from clinical trials and post-marketing data. *Semin Arthritis Rheum* 46(2):238-245, 2016. [S]

Jimenez-Lozano I, Caro-Teller JM, Fernandez-Hidalgo N, Miarons M, Frick MA, Batllori Badia E, Serrano B, Parramon-Teixido CJ, Camba-Longueira F, Moral-Pumarega MT, San Juan-Garrido R, Cabanas Poy MJ, Suy A, Gorgas Torner MQ: Safety of tocilizumab in COVID-19 pregnant women and their newborn: a retrospective study. *J Clin Pharm Ther* 46(4):1062-1070, 2021. [S]

Nakajima K, Watanabe O, Mochizuki M, Nakasone A, Ishizuka N, Murashima A: Pregnancy outcomes after exposure to tocilizumab: a retrospective analysis of 61 patients in Japan. *Mod Rheumatol* 26(5):667-671, 2016. [S]

San-Juan R, Barbero P, Fernandez-Ruiz M, Lopez-Medrano F, Lizasoain M, Hernandez-Jimenez P, Silva JT, Ruiz-Ruigomez M, Corbella L, Rodriguez-Goncer I, Folgueira MD, Lalueza A, Batllori E, Mejia I, Forcen L, Lumbreras C, Garcia-Burguillo A, Galindo A, Aguado JM: Incidence and clinical profiles of COVID-19 pneumonia in pregnant women: a single-centre cohort study from Spain. *EClinicalMedicine* 23:100407, 2020. [E]

Weber-Schoendorfer C, Schaefer C: Pregnancy outcome after tocilizumab therapy in early pregnancy-a case series from the German Embryotox Pharmacovigilance Center. *Reprod Toxicol* 60:29-32, 2016. [S]

THE OTIS AUTOIMMUNE DISEASES IN PREGNANCY PROJECT

The Organization of Teratology Information Services (OTIS) is conducting a nationwide, prospective study in an effort to gain additional information regarding autoimmune diseases, their treatment during pregnancy, and the potential effects of the treatment on the developing embryo or fetus.

Women within their first 19 weeks of pregnancy, living in the United States or Canada, who have an autoimmune disease, and who may or may not be using medication are eligible to enroll. All information collected will remain strictly confidential. Identity of the women and their children will not be used in any report or publication and all files are kept in a locked cabinet.

The coordinating center for the study is located at the University of California, San Diego Medical Center in the Department of Pediatrics. The medical director is Dr. Kenneth Lyons Jones, a pediatrician and specialist in birth defects. More information about the study can be found at the MotherToBaby (OTIS) website: <https://mothertobaby.org/pregnancy-studies/>

Contact Information for Referrals: MotherToBaby (OTIS)

Phone: 1-877-311-8972 (toll-free)

Email: mothertobaby@health.ucsd.edu

Referral forms can be obtained at: <https://mothertobaby.org/refer-patient-form/>