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Drug Interactions:

"7 DRUG INTERACTIONS 7.1 Concomitant Drugs for Treatment of Adult Indications In RA patients, population pharmacokinetic analyses did not detect any effect of methotrexate (MTX), non-steroidal anti-inflammatory drugs or corticosteroids on tocilizumab clearance. Concomitant administration of a single intravenous dose of 10 mg/kg tocilizumab with 10-25 mg MTX once weekly had no clinically significant effect on MTX exposure. Tocilizumab products have not been studied in combination with biological DMARDs such as TNF antagonists see Dosage and Administration (2.2) . In GCA patients, no effect of concomitant corticosteroid on tocilizumab exposure was observed. 7.2 Interactions with CYP450 Substrates Cytochrome P450s in the liver are down-regulated by infection and inflammation stimuli including cytokines such as IL-6. Inhibition of IL-6 signaling in RA patients treated with tocilizumab products may restore CYP450 activities to higher levels than those in the absence of tocilizumab products leading to increased metabolism of drugs that are CYP450 substrates. In vitro studies showed that tocilizumab has the potential to affect expression of multiple CYP enzymes including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Its effect on CYP2C8 or transporters is unknown. In vivo studies with omeprazole, metabolized by CYP2C19 and CYP3A4, and simvastatin, metabolized by CYP3A4, showed up to a 28% and 57% decrease in exposure one week following a single dose of tocilizumab, respectively. The effect of tocilizumab products on CYP enzymes may be clinically relevant for CYP450 substrates with narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of TOFIDENCE, in patients being treated with these types of medicinal products, perform therapeutic monitoring of effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) and the individual dose of the medicinal product adjusted as needed. Exercise caution when coadministering TOFIDENCE with CYP3A4 substrate drugs where decrease in effectiveness is undesirable, e.g., oral contraceptives, lovastatin, atorvastatin, etc. The effect of tocilizumab products on CYP450 enzyme activity may persist for several weeks after stopping therapy see Clinical Pharmacology (12.3) . 7.3 Live Vaccines Avoid use of live vaccines concurrently with TOFIDENCE see Warnings and Precautions (5.9) ."

Precautions:
No information available

Description:

"11 DESCRIPTION Tocilizumab-bavi is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody of the immunoglobulin IgG1 (gamma 1, kappa) subclass with a typical H 2 L 2 polypeptide structure. Each light chain and heavy chain consists of 214 and 448 amino acids, respectively. The four polypeptide chains are linked intra- and inter-molecularly by disulfide bonds. Tocilizumab-bavi has a molecular weight of approximately 148 kDa. The antibody is produced in mammalian (Chinese hamster ovary) cells. Intravenous Infusion TOFIDENCE (tocilizumab-bavi) injection is a sterile, clear to opalescent, colorless to light yellow, preservative-free solution for further dilution prior to intravenous infusion with a pH of approximately 6.2. Each single-dose vial, formulated in an aqueous solution, is available at a concentration of 20 mg/mL containing 80 mg/4 mL, 200 mg/10 mL, or 400 mg/20 mL of TOFIDENCE. Each mL of solution contains arginine hydrochloride (10.53 mg), histidine (0.81 mg), L-histidine hydrochloride monohydrate (1.01 mg), polysorbate 80 (0.5 mg), sucrose (20 mg), and water for injection."

Indications and Usage:

"1 INDICATIONS AND USAGE TOFIDENCE™ (tocilizumab-bavi) is an interleukin-6 (IL-6) receptor antagonist indicated for treatment of: Rheumatoid Arthritis (RA) (1.1) Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs). Giant Cell Arteritis (GCA) (1.2) Adult Patients with giant cell arteritis.. Polyarticular Juvenile Idiopathic Arthritis (PJIA) (1.3) Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis. Systemic Juvenile Idiopathic Arthritis (SJIA) (1.4) Patients 2 years of age and older with active systemic juvenile idiopathic arthritis. Coronavirus Disease 2019 (COVID-19) (1.5) Hospitalized adult patients with coronavirus disease 2019 (COVID-19) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). 1.1 Rheumatoid Arthritis (RA) TOFIDENCE (tocilizumab-bavi) is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs). 1.2 Giant Cell Arteritis (GCA) TOFIDENCE™ (tocilizumab-bavi) is indicated for the treatment of giant cell arteritis (GCA) in adult patients. 1.3 Polyarticular Juvenile Idiopathic Arthritis (PJIA) TOFIDENCE™ (tocilizumab-bavi) is indicated for the treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. 1.4 Systemic Juvenile Idiopathic Arthritis (SJIA) TOFIDENCE™ (tocilizumab-bavi) is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older. 1.5

Coronavirus Disease 2019 (COVID-19) TOFIDENCE™ (tocilizumab-bavi) is indicated for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adult patients who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)."

Warnings:
No information available

Pregnancy:

"8.1 Pregnancy Risk Summary The limited available data with tocilizumab products in pregnant women are not sufficient to determine whether there is a drug-associated risk for major birth defects and miscarriage. Monoclonal antibodies, such as tocilizumab products, are actively transported across the placenta during the third trimester of pregnancy and may affect immune response in the in utero exposed infant see Clinical Considerations . In animal reproduction studies, intravenous administration of tocilizumab to Cynomolgus monkeys during organogenesis caused abortion/embryo-fetal death at doses 1.25 times and higher than the maximum recommended human dose by the intravenous route of 8 mg per kg every 2 to 4 weeks. The literature in animals suggests that inhibition of IL-6 signaling may interfere with cervical ripening and dilatation and myometrial contractile activity leading to potential delays of parturition see Data . Based on the animal data, there may be a potential risk to the fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. Clinical Considerations Fetal/Neonatal adverse reactions Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to TOFIDENCE in utero see Warnings and Precautions (5.9) . Data Animal Data An embryo-fetal developmental toxicity study was performed in which pregnant Cynomolgus monkeys were treated intravenously with tocilizumab at daily doses of 2, 10, or 50 mg/ kg during organogenesis from gestation day (GD) 20-50. Although there was no evidence for a teratogenic/dysmorphogenic effect at any dose, tocilizumab produced an increase in the incidence of abortion/embryo-fetal death at doses 1.25 times and higher the MRHD by the intravenous route at maternal intravenous doses of 10 and 50 mg/ kg. Testing of a murine analogue of tocilizumab in mice did not yield any evidence of harm to offspring during the pre- and postnatal development phase when dosed at 50 mg/kg intravenously

with treatment every three days from implantation (GD 6) until post-partum day 21 (weaning). There was no evidence for any functional impairment of the development and behavior, learning ability, immune competence and fertility of the offspring. Parturition is associated with significant increases of IL-6 in the cervix and myometrium. The literature suggests that inhibition of IL-6 signaling may interfere with cervical ripening and dilatation and myometrial contractile activity leading to potential delays of parturition. For mice deficient in IL-6 (Il6 -/- null mice), parturition was delayed relative to wild-type (Il6 +/+) mice. Administration of recombinant IL-6 to Il6 -/- null mice restored the normal timing of delivery."

Overdosage:

"10 OVERDOSAGE There are limited data available on overdoses with tocilizumab products. One case of accidental overdose was reported with intravenous tocilizumab in which a patient with multiple myeloma received a dose of 40 mg per kg. No adverse drug reactions were observed. No serious adverse drug reactions were observed in healthy volunteers who received single doses of up to 28 mg per kg, although all 5 patients at the highest dose of 28 mg per kg developed dose-limiting neutropenia. In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate symptomatic treatment."