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Ivacaftor

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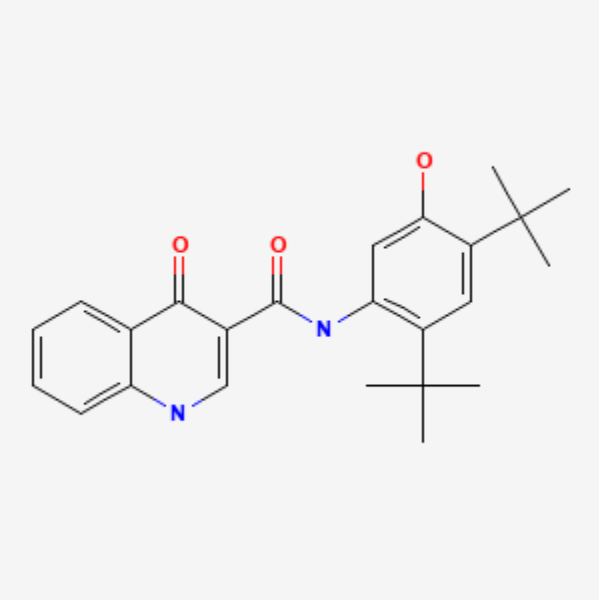

Drug Levels and Effects

Summary of Use during Lactation

Information from one maternal-infant pair with ivacaftor and lumacaftor indicates that maternal ivacaftor therapy produce low levels in milk. An international survey of cystic fibrosis centers found no adverse effects in breastfed infants of mothers taking these drugs. A task force respiratory experts from Europe, Australia and New Zealand found that these drugs are probably safe during breastfeeding.[1] One breastfed infant had transient elevations in bilirubin and liver enzymes during maternal therapy that could not definitively be attributed to the drugs in breastmilk. Until more data are available, monitoring of infant bilirubin and liver enzymes might be advisable during breastfeeding with maternal ivacaftor therapy.[2] Congenital cataracts in breastfed infants has been reported in the infants of mothers who took the drug during pregnancy. Examination of breastfed infants

for cataracts has been recommended.[3] Anecdotal evidence indicates that the drugs in breastmilk may moderate cystic fibrosis in breastfed infants.

Drug Levels

Maternal Levels. A woman with cystic fibrosis was treated with lumacaftor and ivacaftor during pregnancy and postpartum. The dosage was not stated, but it was probably the standard dosage of lumacaftor 400 mg and ivacaftor 250 mg orally every 12 hours. The average concentration of ivacaftor in breastmilk samples taken randomly over a 6-month period without regard to the times of the doses was 35.3 mcg/L (0.09 micromolar).[4]

Two nursing mothers with cystic fibrosis who were taking elexacaftor, ivacaftor and tezacaftor, had their milk samples analyzed 2 or 3 times between 15 and 60 days postpartum. Milk levels were all <1 micromolar in one woman at 15 and 60 days postpartum. The other woman had milk ivacaftor levels of <1 micromolar at 30 days postpartum. Milk levels of all drugs tended to increase slightly over time.[5]

Two nursing mothers with cystic fibrosis were taking elexacaftor, ivacaftor and tezacaftor in unspecified dosages. The ivacaftor concentrations in milk at unreported times after a dose were 0.03 micromolar (11.8 mcg/L) and 0.26 micromolar (102 mcg/L).[6]

A woman with cystic fibrosis received elexacaftor 100 mg, tezacaftor, 50 mg, ivacaftor 75 mg and additional ivacaftor 150 mg daily while exclusively breastfeeding her 3-month-old infant. Fasting breastmilk samples were collected 12 hours after the last dose of ivacaftor 150 mg and before the morning dose of elexacaftor, tezacaftor, and ivacaftor. The concentration of ivacaftor in milk was 1795 mcg/L.[7]

Infant Levels. An infant was breastfed by a mother taking lumacaftor and ivacaftor. The percentage of breastfeeding varied between 25% and 100% during this time period. The average infant ivacaftor plasma concentration over the first 6 months of life, excluding day 1 postpartum, was 3.9 mcg/L (0.01 micromolar). This value corresponded to average of 0.5% of simultaneous maternal plasma levels.[4]

Two partially breastfed (extent not stated) infants whose mothers were taking elexacaftor, ivacaftor and tezacaftor had serum drug concentrations measured several times. Ivacaftor levels were between 0.1 and 1 micromolar at birth and dropped to 0.1 micromolar and below over time.[5]

A woman with cystic fibrosis received elexacaftor 100 mg, tezacaftor, 50 mg, ivacaftor 75 mg and additional ivacaftor 150 mg daily while exclusively breastfeeding her 3-month-old infant. An infant blood sample was collected 12 hours after the last dose of ivacaftor 150 mg and before the morning dose of elexacaftor, tezacaftor, and ivacaftor. The infant was not breastfed 2 hours prior to blood collection. The infant plasma concentration of ivacaftor was 23.9 mcg/L.[7]

Effects in Breastfed Infants

A woman with cystic fibrosis was treated with lumacaftor and ivacaftor during pregnancy and postpartum. Her infant was fully breastfed until day 29 postpartum when elevated direct and indirect bilirubin, aspartate aminotransferase (AST), and alkaline phosphatase were found to be elevated. All values had been normal on days 1 and 14. The fraction of breastmilk the infant received was reduced to 25% and all values were normal on day 37. The fraction of breastfeeding was increased to 50% and then to 100%. On day 135, the infant's direct bilirubin was elevated during concurrent maternal levofloxacin and trimethoprim-sulfamethoxazole therapy. The fraction of breastfeeding was decreased to 75% and the direct bilirubin was normal on day 154. The authors noted that the abnormal test results could not definitively be attributed to lumacaftor and ivacaftor therapy.[4]

A survey was sent to lead clinicians of adult CF centers in Europe, the United Kingdom, United States of America, Australia and Israel requesting anonymized data on pregnancy outcomes in women using CFTR modulators during pregnancy and lactation. Responses were received from 31 centers and one woman with CF

for a total of 64 pregnancies in 61 women resulting in 60 live births. Thirteen infants were breastfed on ivacaftor alone, 9 infants were breastfed on lumacaftor and ivacaftor, and 5 infants were breastfed on tezacaftor and ivacaftor for a total of 27 infants exposed to ivacaftor in breastmilk, all with no reported complications. The extent of breastfeeding was not reported.[7] An updated survey by the same authors asked CF clinicians to report on pregnant women exposed to the elexacaftor, tezacaftor and ivacaftor combination during pregnancy and breastfeeding. Twenty-six infants were breastfed (extent not stated) during maternal use of the combination. No adverse effects were reported in the breastfed infants.[8]

An infant was born to a mother taking elexacaftor, ivacaftor and tezacaftor for cystic fibrosis. The infant was breastfed (extent not stated). Although the infant had cystic fibrosis-causing *CFTR* mutations, the infant was healthy and tested negative for cystic fibrosis on newborn screening. The authors expressed concern that the drugs received transplacentally and in breastmilk caused a false negative screening test.[9]

A mother who was a heterozygous carrier of the F508del gene became pregnant with a homozygous infant. At 32 weeks of pregnancy, the mother began elexacaftor, ivacaftor and tezacaftor in the usual adult dosage to treat her fetus who had evidence of meconium ileus. The infant was born at 36 weeks and given pancreatic enzyme replacement therapy with breastfeeding while maternal treatment continued. The infant's fecal elastase, transaminases and bilirubin were normal at about 1 month of age. The infant's sweat chloride, although low, was nearer to normal than was expected. The authors hypothesized that the medications received in breastmilk moderated the disease process in the infant.[10]

Three women with cystic fibrosis were taking elexacaftor, ivacaftor and tezacaftor in unspecified dosages during pregnancy and postpartum while breastfeeding. On routine visual examinations between 8 days and 6 months postpartum, their infants were found to have small (<1.0 mm) bilateral cataracts, in the central area in one and outside the visual axis in the other two. Breastfeeding was discontinued after diagnosis at 16 days, 9 weeks and 6 months postpartum. The contribution of breastfeeding to the cataracts could not be determined.[6]

Two women were reported by the British Columbia cystic fibrosis clinic who became pregnant and breastfed their infants. One took ivacaftor and breastfed (extent not stated) for 42 months. Her infant was physically normal and healthy, but had speech delay. The other woman took Tricafta (ivacaftor, elexacaftor, and tezacaftor). She breastfed (extent not stated) her infant for 6 months and her infant had no complications.[11]

A woman with cystic fibrosis took ivacaftor 150 mg, tezacaftor 100 mg and elexacaftor 200 mg in the morning and ivacaftor 150 mg at night during pregnancy and breastfeeding (extent not stated). The infant had not regained his birthweight at 10 days postpartum, his stools had a greasy rim and he had pancreatic elastase levels below levels for pancreatic sufficiency but higher than usually expected for newborns homozygous for this mutation. The infant was started on pancreatic enzymes and by day 20, he had normal elastase levels. By day 45 of life was gaining weight and stools were normal. At 6 months of age the infant was still being breastfed and doing well. The authors felt that when breastfeeding is stopped, a rebound in symptoms might occur because the infant will no longer be receiving small amounts of the mother's medications through milk.[12]

A woman with cystic fibrosis received elexacaftor 100 mg, tezacaftor, 50 mg, ivacaftor 75 mg and additional ivacaftor 150 mg daily from 12 weeks of pregnancy and postpartum. The mother exclusively breastfed her infant while continuing therapy, and no significant side effects related were observed in the infant up to at least 3 months of age.[13]

Effects on Lactation and Breastmilk

Relevant published information was not found as of the revision date.

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Substance Identification

Substance Name

Ivacaftor

CAS Registry Number

873054-44-5

Drug Class

Breast Feeding

Lactation

Milk, Human

Chloride Channel Agonists

Cystic Fibrosis Transmembrane Conductance Regulator Protein Modulator

CFTR Protein Modulator