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רופא/ה, רוקח/ת נכבד/ה,
ברצוננו להודיעך על עדכון בעלון לרופא של **Torisel :**

Renal cell carcinoma:
Torisel is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC) Mantle Cell lymphoma.
Torisel is indicated for the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (MCL).

להלן העדכונים העיקריים בעלון לרופא:

2. Qualitative And Quantitative Composition

Excipients with known effect:

Ethanol

- 1 vial of concentrate contains 474 mg of anhydrous ethanol which is equivalent to 394.6 mg/ml (39.46% w/v).
  1.8 ml of the diluent provided contains 358 mg anhydrous ethanol which is equivalent to 199.1 mg/ml (19.91% w/v).

Propylene glycol

- 1 vial of concentrate contains 604 mg of propylene glycol which is equivalent to 503.3 mg/ml (50.33% w/v).

4.4 Special warnings and precautions for use

1.1 Excipient information

Ethanol

After first dilution the concentrate with 1.8 ml of the supplied diluent, the concentrate-diluent mixture contains 35% volume ethanol (alcohol), i.e., up to 0.693 g per 25 mg dose of temsirolimus, equivalent to 18 ml beer or 7 ml wine per dose. Patients administered the higher dose of 175 mg of temsirolimus for the initial treatment of MCL may receive up to 4.85 g of ethanol (equivalent to 122 ml beer or 49 ml wine per dose).

An example of ethanol exposure based on maximum single daily dose (see section 4.2) is as follows:

- Administration of the higher dose of 175 mg of temsirolimus for the initial treatment of MCL to an adult weighing 70 kg would result in exposure to 69.32 mg/kg of ethanol which may cause a rise in blood alcohol concentration (BAC) of about 11.5 mg/100 ml.

For comparison, for an adult drinking a glass of wine or 500 ml of beer, the BAC is likely to be about 50 mg/100 ml.

The amount of ethanol in this medicine is not likely to have an effect in adults and adolescents, and its effects in children are not likely to be noticeable. It may have some effects, such as somnolence, in neonates and young children.

The ethanol content in this medicinal product should be carefully considered in the following patient groups who may be at higher risk of ethanol-related adverse effects:

- Pregnant or breast-feeding women (see section 4.6)
- Patients suffering from alcoholism.

To be taken into account in pregnant or breast-feeding women, children and high-risk groups, such as patients with liver disease or epilepsy. The amount of alcohol in this medicinal product may alter the effects of other medicines.
Co-administration with medicines containing e.g. propylene glycol or ethanol may lead to accumulation of ethanol and induce adverse effects, particularly in young children with low or immature metabolic capacity.

The amount of alcohol in this medicinal product may impair the ability to drive or use machines (see section 4.7).

Propylene glycol
Torisel contains propylene glycol (see section 2). An example of propylene glycol exposure based on maximum single daily dose (see section 4.2) is as follows: Administration of the higher dose of 175 mg of temsirolimus for the initial treatment of MCL to an adult weighing 70 kg would result in a propylene glycol exposure of 50.33 mg/kg/day.

Medical monitoring, including measurement of the osmolar and/or anion gap, is required in patients with impaired renal and/or hepatic function who receive ≥50 mg/kg/day of propylene glycol. Various adverse effects attributed to propylene glycol have been reported, such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction.

Prolonged administration of propylene glycol-containing products, as well as co-administration with other substrates of alcohol dehydrogenase (e.g. ethanol), increase the risk of propylene glycol accumulation and toxicity, especially in patients with liver or kidney impairment.

Propylene glycol doses of ≥1 mg/kg/day may induce serious adverse effects in neonates, while doses of ≥50 mg/kg/day may induce adverse effects in children less than 5 years old and should only be administered on a case by case basis.

Administration of ≥50 mg/kg/day of propylene glycol to pregnant or lactating women should only be considered on a case by case basis (see section 4.6).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Due to the unknown risk related to potential exposure during early pregnancy, women of childbearing potential must be advised not to become pregnant while using Torisel.

Men with partners of childbearing potential should use medically acceptable contraception while receiving Torisel (see section 5.3).

Pregnancy

There are no adequate data from the use of temsirolimus in pregnant women. Studies in animals have shown reproductive toxicity. In reproduction studies in animals, temsirolimus caused embryo/foetotoxicity that was manifested as mortality and reduced foetal weights (with associated delays in skeletal ossification) in rats and rabbits. Teratogenic effects (omphalocele) were seen in rabbits (see section 5.3).

The potential risk for humans is unknown. Torisel must not be used during pregnancy, unless the risk for the embryo is justified by the expected benefit for the mother. The ethanol content of this product should also be taken into account for pregnant women (see section 4.4).

Torisel contains propylene glycol (see section 4.4). Propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, however, it may reach the foetus. Administration of ≥50 mg/kg/day propylene glycol to pregnant women should only be considered on a case by case basis.

Breast-feeding

It is unknown whether temsirolimus is excreted in human breast milk. The excretion of temsirolimus in milk has not been studied in animals. However, sirolimus, the main metabolite of temsirolimus, is excreted in milk of lactating rats. Because of the potential for adverse reactions in breast-fed infants from temsirolimus, breast-feeding should be discontinued during therapy. The ethanol content of this product should be taken into account in women who are breast-feeding (see section 4.4).

Torisel contains propylene glycol (see section 4.4). Propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, however, it has been found in milk and may be orally absorbed by a nursing infant. Administration of ≥50 mg/kg/day propylene glycol to lactating women should only be considered on a case by case basis.

Fertility

In male rats, decreased fertility and partly reversible reductions in sperm counts were reported (see section 5.3).

בברכה,
אורטל עבודי
רוקחת ממונה