

הודעה על החמרה (מידע בטיחות) בעלון לרופא

תאריך: 27/11/2011

שם תכשיר באנגלית: TORISEL

מספר רישום : 143-18-32044-00

שם בעל הרישום : Neopharm Ltd.

ההחמרות סומנו בצהוב

פרטים על השינויים המבוקשים

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טקסט חדש	טקסט נוכחי	פרק בעלון

Paediatric population

There is no relevant use of temsirolimus in the paediatric population in the indication: treatment of renal cell carcinoma and mantle cell lymphoma. Temsirolimus should not be used in the paediatric population for the treatment of neuroblastoma, rhabdomyosarcoma or high-grade glioma, because of efficacy concerns based on the available data (see section 5.1).

Method of administration

TORISEL must be administered by intravenous (IV) infusion. For instructions on dilution and preparation of the medicinal product before administration, see section 6.6.

Hepatic impairment

Use caution when treating patients with hepatic impairment.

Temsirolimus is cleared predominantly by the liver. In an open-label, dose-escalation phase I study in 110 subjects with advanced malignancies and either normal or impaired hepatic function, concentrations of temsirolimus and its metabolite sirolimus were increased in patients with elevated AST or bilirubin levels. Assessment of AST and bilirubin levels is recommended before initiation of temsirolimus and periodically after.

An increased rate of fatal events was observed in patients with moderate and severe hepatic impairment. The fatal events included those due to progression of disease; however a causal relationship cannot be excluded.

Interstitial lung disease

There have been cases of non-specific interstitial pneumonitis, including fatal reports, occurring in patients who received weekly intravenous TORISEL. Some patients were asymptomatic or had minimal symptoms with pneumonitis detected on computed tomography scan or chest radiograph. Others presented with symptoms such as dyspnoea, cough, and fever. Some patients required discontinuation of TORISEL or treatment with corticosteroids and/or antibiotics, while some patients continued treatment without additional intervention. It is recommended that patients undergo baseline radiographic assessment by lung computed tomography scan or chest radiograph prior to the initiation of TORISEL therapy. Periodical follow-up assessments may be considered. It is recommended that patients be followed closely for occurrence of clinical respiratory symptoms and patients should be advised to report promptly any new or worsening

Paediatric population

Experience in paediatric patients is limited. The safety and effectiveness in paediatric patients have not been established. Therefore, the use of TORISEL in the paediatric population is not recommended until further information on effectiveness and safety is available.

Posology and method of administration

Hepatic impairment

Temsirolimus is cleared predominantly by the liver. Based on an open-label, dose-escalation study in 112 subjects with advanced malignancies and either normal or impaired hepatic function,

Special warnings and precautions for use

Interstitial lung disease

There have been cases of non-specific interstitial pneumonitis, including rare fatal reports, occurring in patients who received weekly intravenous TORISEL. Some patients were asymptomatic with pneumonitis detected on computed tomography scan or chest radiograph. Others presented with symptoms such as dyspnoea, cough, and fever. Some patients required discontinuation of TORISEL or treatment with corticosteroids and/or antibiotics, while some patients continued treatment without additional intervention. Patients should be followed for clinical respiratory symptoms.

respiratory symptoms. If clinically significant respiratory symptoms develop, consider withholding TORISEL administration until after recovery of symptoms and improvement of radiographic findings related to pneumonitis. Empiric treatment with corticosteroids and/or antibiotics may be considered.

Excipients

After first dilution of TORISEL 30 mg concentrate with 1.8 ml of withdrawn diluent, the concentrate-diluent mixture contains 35% volume ethanol (alcohol); i.e., up to 0.693 g per 25 mg dose of TORISEL, equivalent to 17.6 ml beer, 7.3 ml wine per dose. Patients administered the higher dose of 175 mg of TORISEL for the initial treatment of MCL may receive up to 4.85 g of ethanol (equivalent to 123 ml beer, 51 ml wine per dose).

Harmful for those 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. The amount of alcohol in this medicinal product may impair your ability to drive or use machines.

Excipients

This medicinal product (concentrate-diluent mixture) contains 35% volume ethanol (alcohol); i.e., up to 693.5 mg per dose, equivalent to 17.6 ml beer, 7.3 ml wine per dose.

Harmful for those 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.

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.

Fertility

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

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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.

Fertility, Pregnancy and Lactation

For patients receiving the higher dose of 175 mg IV of TORISEL for the treatment of MCL, the amount of ethanol in this medicinal product may impair your ability to drive or use machines (see section 4.4).

Effects on ability to drive and use machines

Post Marketing Experience

There have been reports of Stevens-Johnson syndrome in patients who received TORISEL.

There have been reports of rhabdomyolysis in patients who received TORISEL.

Paediatric population

In a phase 1/2 study, 71 patients (59 patients, aged from 1 to 17 years old, and 12 patients, aged 18 to 21 years) were administered temsirolimus at doses ranging from 10 mg/m² to 150 mg/m² (see section 5.1).

The adverse reactions reported by the highest percentage of patients were haematologic (anaemia, leukopaenia, neutropaenia, and thrombocytopaenia), metabolic (hypercholesterolaemia, hyperlipaemia, hyperglycaemia, increase of serum aspartate amino transferase [AST] and serum alanine aminotransferase [ALT] plasma levels), and digestive (mucositis, stomatitis, nausea, and vomiting).

Undesirable effects

pharmacodynamic properties

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Paediatric population

In a phase 1/2 safety and exploratory efficacy study, 71 patients (59 patients, aged from 1 to 17 years, and 12 patients, aged from 18 to 21 years) received temsirolimus as a 60-minute IV infusion once weekly in three-week cycles. In part 1, 14 patients aged from 1 to 17 years with advanced recurrent/refractory solid tumours received temsirolimus at doses ranging from 10 mg/m² to 150 mg/m². In part 2, 45 patients aged from 1 to 17 years with recurrent/relapsed rhabdomyosarcoma, neuroblastoma, or high grade glioma were administered temsirolimus at a weekly dose of 75 mg/m². Adverse events were generally similar to those observed in adults (see section 4.8).

Temsirolimus was found to be ineffective in paediatric patients with neuroblastoma,

Pharmacological properties-

rhabdomyosarcoma, and high-grade glioma (n = 52). For subjects with neuroblastoma, the objective response rate was 5.3% (95% CI: 0.1%, 26.0%). After 12 weeks of treatment, no response was observed in subjects with rhabdomyosarcoma or high-grade glioma. None of the 3 cohorts met the criterion for advancing to the second stage of the Simon 2-stage design.

Pharmacokinetic properties

Hepatic impairment

Temsirolimus should be used with caution when treating patients with hepatic impairment.

Temsirolimus is cleared predominantly by the liver.

Temsirolimus and sirolimus pharmacokinetics have been investigated in an open-label, dose-escalation study in 110 patients with advanced malignancies and either normal or impaired hepatic function. For 7 patients with severe hepatic impairment (ODWG, group D) receiving the 10 mg dose of temsirolimus, the mean AUC of temsirolimus was ~1.7-fold higher compared to 7 patients with mild hepatic impairment (ODWG, group B). For patients with severe hepatic impairment, a reduction of the temsirolimus dose to 10 mg is recommended to provide temsirolimus plus sirolimus exposures in blood (mean AUC_{sum} approximately 6510 ng·h/ml; n=7), which approximate to those following the 25 mg dose (mean AUC_{sum} approximately 6580 ng·h/ml; n=6) in patients with normal liver function (see sections 4.2 and 4.4).

The AUC_{sum} of temsirolimus and sirolimus on day 8 in patients with mild and moderate hepatic impairment receiving 25 mg temsirolimus was similar to that observed in patients without hepatic impairment receiving 75 mg (mean AUC_{sum} mild: approximately 9770 ng·h/ml, n=13; moderate: approximately 12380 ng·h/ml, n=6; normal approximately 10580 ng·h/ml, n=4).

Paediatric population

In the paediatric population, clearance of temsirolimus was lower and exposure (AUC) was higher than in adults. In contrast, exposure to sirolimus was commensurately reduced in paediatric patients, such that the net exposure as measured by the sum of temsirolimus and sirolimus AUCs (AUC_{sum}) was comparable to that for adults.

Hepatic impairment

Temsirolimus and sirolimus pharmacokinetics have been investigated in an open-label, dose-escalation study in 112 patients with advanced malignancies and either normal or impaired hepatic function. For 7 patients with severe hepatic impairment (ODWG, group D) receiving the 10 mg dose of temsirolimus, the mean AUC of temsirolimus was ~1.7-fold higher compared to 6 patients with mild hepatic impairment (ODWG, group B). For patients with severe hepatic impairment, a reduction of the temsirolimus dose to 10 mg is recommended to provide levels of temsirolimus and sirolimus exposures in blood (AUC_{sum} 6580 ng·h/ml), which approximate to those following the 25 mg dose (AUC_{sum} 7280 ng·h/ml) in patients with normal liver function (see sections 4.2 and 4.4).

Paediatric population

Temsirolimus and sirolimus pharmacokinetics in the paediatric population have not been investigated.

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