TORISEL® (temsirolimus)
Use in Patients with Renal Dysfunction

SUMMARY

- No dose adjustment of temsirolimus is recommended in patients with renal impairment\(^1,2\).
- Temsirolimus elimination by the kidneys is negligible\(^1,2\).
- Renal failure (including fatal outcomes) has been observed in patients receiving Torisel for advanced renal cell cancer and/or with pre-existing renal insufficiency\(^1,2\).
- Following a 25mg intravenous (IV) dose of [14C]-labelled temsirolimus in six healthy male subjects, 78% of radioactivity was recovered from faeces, and less than 5% of total radioactivity was excreted in the urine\(^3\).
- A population based analysis concluded that there is no pharmacokinetic basis for modifying the temsirolimus dose in patients with renal cell carcinoma (RCC)\(^4,5\).
- Results from a safety analysis of temsirolimus showed an increased incidence of rash and higher dose interruption rates in patients with renal insufficiency compared to those without renal insufficiency\(^6\).
- Limited data on the pharmacokinetics of temsirolimus in patients undergoing haemodialysis suggests temsirolimus is not significantly affected by haemodialysis\(^7,8\).
- This letter regarding Torisel includes information of an off-label nature. Pfizer does not suggest or recommend the use of Torisel in any manner other than as described in the Product Labelling.

INTRODUCTION

Temsirolimus inhibits mammalian target of rapamycin (mTOR) kinase, which regulates cell growth, proliferation and angiogenesis.

RELEVANT LABELLING DATA

The Torisel Summary of Product Characteristics (SPC)\(^1\) and the Torisel Local Product Labelling Document of Switzerland\(^2\) provide the following information regarding patients with renal dysfunction:

Renal impairment

No dose adjustment of temsirolimus is recommended in patients with renal impairment. Temsirolimus should be used with caution in patients with severe renal impairment.

Temsirolimus elimination by the kidneys is negligible; studies in patients with varying renal impairment have not been conducted. Torisel has not been studied in patients undergoing haemodialysis.

Renal failure

Renal failure (including fatal outcomes) has been observed in patients receiving Torisel for advanced renal cell cancer and/or with pre-existing renal insufficiency.
For further information regarding indications, dosage and administration, contraindications, warnings and precautions, interactions and adverse effects please refer to the local product labelling of Torisel.

PUBLISHED DATA

As of September 12, 2011, a detailed search of the published medical literature has identified several articles that discuss the use of temsirolimus in patients with renal dysfunction. A review of some of these articles follows.

Excretion of Radio-Labelled Temsirolimus

Twelve healthy male volunteers received one dose of oral (n=6) or intravenously (IV) (n=6) \([^{14}\text{C}]-\text{temsirolimus}\) in doses of 30mg and 25mg respectively. Excretions were collected and analysed for amount of radioactivity present. Renal excretion accounted for 4.6% of the \([^{14}\text{C}]-\text{temsirolimus}\) administered IV in six patients. Faecal elimination was the predominant pathway and urinary excretion was low. Based on this analysis, it was concluded that renal elimination plays only a minor role in the clearance of temsirolimus and its predominant metabolite, sirolimus\(^3\).

Population Pharmacokinetic Analysis

A pooled pharmacokinetic analysis of temsirolimus was conducted to determine whether standard demographic factors such as age, weight, sex, and race could contribute to variability of pharmacokinetic parameters. Creatinine clearance was also assessed to indirectly detect the possible effects of renal impairment on drug disposition. This analysis merged pharmacokinetic data collected from two phase 1 trials and two phase 2 trials. The samples analysed were collected from 195 patients with advanced renal cell or locally advanced or metastatic breast cancer and 30 healthy volunteers following IV administration of temsirolimus at doses ranging from 1-250mg. Participants in these studies had creatinine clearance values between 34.2-162ml/min/70kg\(^4,5\).

A covariate analysis was conducted on the samples from these 225 patients. No significant effect on pharmacokinetic parameters was observed for the creatinine clearance value. According to this data, no dosage adjustment is required for temsirolimus based on patient creatinine clearance\(^4,5\).

Clinical Experience

In a published abstract from the 2009 American Society of Clinical Oncology (ASCO) annual meeting, Gupta \textit{et al} reported results from a safety analysis of temsirolimus and everolimus in patients with renal insufficiency. Eleven patients with a calculated creatinine clearance (CrCl) of \(\leq 60\) mL/min (average of 42 mL/min) and 13 patients with a calculated CrCl > 60 mL/min received either temsirolimus or everolimus. Safety and efficacy data was collected and analyzed with respect to renal function. An increased incidence of mild to moderate rash (45% versus 15%) and higher dose interruption rates (64% versus 38%) were observed in patients with renal insufficiency compared to those without renal insufficiency, respectively\(^6\).
Haemodialysis

Lunardi et al conducted a pharmacokinetic study in two patients receiving temsirolimus for metastatic RCC who were on haemodialysis. Both patients received temsirolimus 25mg IV as a 30-minute infusion and were pre-treated with diphenhydramine 25mg (IV anti-histamine) 30 minutes prior to the start of each temsirolimus infusion to prevent acute hypersensitivity reactions. Both patients underwent haemodialysis 24, 72 and 144 hours after temsirolimus infusion.

During the first week of treatment, whole blood samples were obtained prior to haemodialysis at 24, 72 and 144 hours. Whole blood samples were then obtained and evaluated for pharmacokinetic parameters at 0 (pre-dose), 0.5 (end of infusion), 1.5, 2.5, and 5.5 hours following temsirolimus administration. Three additional whole blood samples were obtained in each of the patients one hour after the end of haemodialysis at 28, 76, and 148 hours to compare drug values before and after haemodialysis. Whole blood samples of temsirolimus and sirolimus were measured by reversed phase high performance liquid chromatography mass spectrometry. Temsirolimus and sirolimus pharmacokinetic data were analysed. The investigators reported mean percent difference between drugs before and after haemodialysis were 6% and 10% for temsirolimus and sirolimus, respectively. Concentrations of temsirolimus and sirolimus immediately before haemodialysis were not statistically different from those obtained 1 hour after haemodialysis.

The authors concluded that the pharmacokinetics of temsirolimus and sirolimus are not significantly affected by haemodialysis and no dosage adjustment or supplementation is required for temsirolimus following haemodialysis.

Lunardi et al compared the pharmacokinetics of temsirolimus and its major metabolite, sirolimus for 11 patients with RCC not receiving dialysis with 2 patients with RCC receiving haemodialysis. A single dose of 25mg of temsirolimus was administered to both groups as a 30 minute IV infusion. Pharmacokinetic profiles were analysed using non-compartmental analysis techniques. No statistical significant difference was observed between the pharmacokinetic parameters of either temsirolimus or sirolimus when comparing between patients receiving haemodialysis and those patients not receiving dialysis.

Although an important finding, the strength of the data presented above is limited due to the sample number of patients studied. No data is currently available on the use of temsirolimus in peritoneal dialysis or continuous haemofiltration.

References:

1. Torisel (temsirolimus). Summary of Product Characteristics, applicable to all countries of the EU and Norway.
2. Torisel (temsirolimus). Local Product Labelling Document (Switzerland)
3. Data on file (CSR-63037, May 2006), Wyeth Research
5. Data on file (CSR-64107, June 2006), Wyeth Research
6. Gupta S et al. Safety and efficacy analysis of sunitinib (S), bevacizumab (B), and M-Tor inhibitors in metastatic renal cell cancer (mRCC) patients (pts) with renal insufficiency (RI) [abstract]. J Clin Oncol 27:15s, 2009. Abstract 5108
8. Lunardi G et al. Comparison of Temsirolimus Pharmacokinetics in Patients with Renal Cell
Carcinoma Not Receiving Dialysis and Those Receiving Haemodialysis: A Case Series Clin Therapeutics 2009;31:1812-1819