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ORIGINAL ARTICLE

Stability of ready-to-use temsirolimus infusion solution (100 mg/L) in polypropylene containers under different storage conditions

Stabilité des solutions de temsirolimus diluées (100 mg/L dans des poches de polypropylène) dans différentes conditions de conservation

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Different storage conditions

Summary The aim of this study was to determine the stability of ready-to-use temsirolimus infusion solutions under different storage conditions. Solutions were prepared in polypropylene containers by adding temsirolimus injection to 0.9% sodium chloride infusion to reach a final concentration of 100 mg/L. The following storage conditions were tested: (i) 4 °C in the refrigerator; (ii) 20 °C under room light exposure and light protection; and (iii) outdoor temperature with sunlight exposure. Moreover, stress testing was performed on drug substance at 20 °C under ultraviolet (UV) radiation (365 nm). A stability-indicating high-performance liquid chromatography (HPLC) method with UV detection was developed for this analysis. Precision was below 4% and accuracy ranged from 97 to 102%. The lower limit of quantitation was 0.1 mg/L. The degradation products produced after UV light exposure were detected upon further analysis by mass spectrometry detection. The stability of temsirolimus is light and temperature dependent. After storage at 20 °C with room light exposure, the rate of degradation was around 0.25%/h; after 1 day, 92.5% of the initial temsirolimus concentration was recovered. When protected from light, at 4 and 20 °C, losses were decelerated; the decrease in drug concentration was 1.0 and 1.56% per day, respectively. Under daylight exposure, a substantial decrease in drug concentration was observed; after 1 h, losses were higher than 10%. Exposed to UV light, half of the drug was lost after 45 min. In conclusion, temsirolimus 100 mg/L in infusion polypropylene bags containing 0.9% sodium chloride was chemically stable when protected from light for 4 and 3 days at 4 and 20 °C, respectively.

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MOTS CLÉS
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Poches en polypropylène ;
Stabilité ;
Différentes conditions de stockage

Résumé L'objectif de cette étude a été de déterminer la stabilité des solutions de temsirolimus après reconstitution dans différentes conditions de conservation. Les solutions ont été préparées dans des flacons en polypropylène en ajoutant le concentré de temsirolimus pour injection à une solution de chlorure de sodium à 0,9 % afin d'obtenir une concentration finale de 100 mg/L. Les conditions suivantes de stockage ont été testées : (i) 4 °C dans le réfrigérateur ; (ii) 20 °C avec et sans exposition à la lumière artificielle ; et (iii) température extérieure avec exposition à la lumière solaire. La stabilité de la solution reconstituée a été également testée à 20 °C sous une lampe à lumière ultraviolette à 365 nm. La stabilité a été mesurée par chromatographie liquide haute performance et détection dans l'ultraviolet (CLHP-UV). La fidélité de la méthode est inférieure à 4 % et l'exactitude varie de 97 à 102 %. La limite de quantification est de 0,1 mg/L. Les produits de dégradation formés après exposition à la lumière ultraviolette ont été analysés par CLHP et détection par spectrométrie de masse. La stabilité du temsirolimus est lumière et température dépendent. Après stockage à 20 °C à la lumière artificielle, la vitesse de dégradation est de l'ordre de 0,25 %/h ; 92,5 % de la concentration initiale de temsirolimus sont retrouvés après un jour de stockage. Protégé de la lumière à 4 et 20 °C, les pertes sont beaucoup moins importantes ; la concentration diminue respectivement de 1,0 et 1,56 %/jour. Exposé à la lumière solaire, une réduction substantielle de la concentration est observée ; après une heure, les pertes sont supérieures à 10 %. Exposé à la lumière ultraviolette, la moitié de la concentration de temsirolimus a disparu après 45 minutes. En conclusion, la solution de temsirolimus à 100 mg/L est stable trois jours à 20 °C protégé de la lumière et quatre jours à 4 °C dans des flacons en polypropylène contenant du chlorure de sodium à 0,9 %.

Introduction

Temsirolimus (sirolimus-42-[2,2-bis-(hydroxymethyl)]-propionate) is an ester analog of rapamycin, a macrolide antibiotic with antifungal, antitumor, and immunosuppressive activities [1]. This compound exists as different diastereoisomers (Fig. 1); regarding stereochemistry, three isomers A, B and C can exist and they interconvert in solution. Isomer B is the predominant isomer ($\geq$ 97%) in both solution and solid states [2,3]. Temsirolimus inhibits the mammalian target of rapamycin (mTOR) kinase, a component of intracellular signaling pathway involved in cell growth and proliferation [4,5], and in the response of such cells to hypoxic stress [6]. Temsirolimus binds to FK506-binding protein 12 (FKBP12), and the resultant protein—drug complex inhibits the kinase activity of mTOR [7,8]. mTOR is a serine/threonine kinase which plays a role in the phosphatidylinositol 3-kinase/AKT pathway that is upregulated in some tumors [4,5,9]. Blockade of mTOR signaling by temsirolimus inhibits the production of proteins that regulate progression to the cell cycle [9,10] and angiogenesis [11,12]. Temsirolimus received approval by the US Food and Drug Administration in May 2007, and by the European Medicines Agency (EMA) in November 2007 for the treatment of advanced renal cell carcinoma. This drug has United Kingdom marketing authorization for the first-line treatment of patients with advanced renal cell carcinoma who have at least three of the six prognostic risk factors [13]. Recently, temsirolimus received approval by EMA in September 2011 for the treatment of adult patients with relapsed or refractory mantle cell lymphoma. The safety, tolerability and efficacy of temsirolimus have been well established in clinical trials [14,15]. Drug related toxicity included rash, mucositis, asthenia, nausea, hyperglycemia, hypophosphatemia, anemia, and hypertriglyceridemia. Clinical activity in other tumor types, such as relapsed or refractory non-Hodgkin lymphoma [16,17], endometrial cancer [18], neuroendocrine carcinomas [19], sarcoma [20], and metastatic breast cancer [21] has been observed. Temsirolimus is therefore an important new agent for cancer treatment.

Temsirolimus is administered as a solution to be given by intravenous infusion over 30 to 60 min. The finished product, Torisel®, is a two-vial system consisting of a concentrate solution containing 25 mg/mL temsirolimus (in one vial) and a specifically formulated diluent (in another vial) composed of polysorbate 80, polyethylene glycol 400, dehydrated alcohol and nitrogen. Before use, the temsirolimus concentrate has to be diluted with the diluent, followed by a dilution with 0.9% sodium chloride for intravenous injection. According to the manufacturer's guidelines for quality assurance, the solution is stable at least 6 h at 25 °C when protected from sunlight and excessive fluorescent light. This short stability prompted us to investigate stability assays that could be useful in clinical practice using a centralized preparation unit.

To our knowledge, no other data are available in the literature concerning the stability of this compound in reconstituted solution. Thus, we undertook to study the effects of temperature and light (room or sunlight) on the stability of temsirolimus over a period of 15 days. The aim of our study was to reproduce the different conditions of use and storage encountered at the hospital pharmacy.

Experimental

Reagents

Temsirolimus (Torisel®) was purchased from Wyeth Pharmaceuticals (Paris, France). Two different reconstituted stock solutions were used; each of them contained 25 g/L of temsirolimus in the diluent. Solution A was used in the