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Contents

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Drugs in R&D™

Aim and Scope: The aim of *Drugs in R&D* is to provide timely information on: (i) emerging drug classes; and (ii) new treatments for specific disorders. Original research from all phases of clinical development is included, with a strong link to clinical practice. Healthcare decision-makers are thus provided with clinically applicable knowledge about the likely place in therapy of a drug.

Journal issues comprise:

- Original research, including clinical trials with an emphasis on optimum clinical use and pharmacokinetic and pharmacodynamic studies in patients and healthy volunteers.
- R&D drug profiles including: (i) key drug properties; (ii) drug development phase by country and indication; (iii) analysis of commercial potential.

All articles are subject to peer review by international experts.

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Temsirolimus

CCI 779, CCI-779, Cell Cycle Inhibitor-779

Abstract

Wyeth (formerly American Home Products) is developing temsirolimus [*Cell cycle inhibitor-779, CCI 779*], an ester analogue of sirolimus, for the treatment of cancer, multiple sclerosis and rheumatoid arthritis. Temsirolimus binds to the cytosolic protein, FKBP, which subsequently inhibits mTOR (mammalian target of rapamycin). Inhibition of mTOR blocks a number of signal transduction pathways that suppress translation of several key proteins regulating the cell cycle. These effects lead to a cell cycle block at the G_1 phase.

In animal models of human cancers, temsirolimus inhibited the growth of a diverse range of cancer types even when an intermittent dosing schedule was used. The compound also appears to have potential for the blockade of inflammatory responses associated with autoimmune and rheumatic diseases by inhibiting T-cell proliferation.

On 11 March 2002, American Home Products changed its name and the name of its subsidiary Wyeth-Ayerst to Wyeth.

During the first half of 2004, Wyeth initiated ongoing recruitment into a US phase III trial comparing orally administered temsirolimus plus letrozole versus letrozole alone as first-line treatment among ≈1200 postmenopausal women with advanced breast cancer. The multicentre, randomised, double-blind, placebo-controlled trial is estimated to last 34 months. All subjects will have the option of participating in the long-term follow-up phase of the trial that involves follow-up every 3 months until disease progression; the primary endpoint is overall progression-free survival.

In August 2004, the US FDA granted temsirolimus fast-track status for the first-line treatment of poor-prognosis patients with advanced renal cell carcinoma.[1]

Previously in March 2002, temsirolimus received fast-track status from the FDA for the treatment of renal cell carcinoma in patients who failed to respond to interleukin-2 treatment. Wyeth intends to file a NDA for temsirolimus for this indication by 2006.[2]

Researchers from Wyeth presented the findings from a preclinical study of temsirolimus at the 67th Annual Scientific Meeting of the American College of Rheumatology and the 38th Annual Meeting Association of Rheumatology Health Professionals (ACR/ARHP-2003) [*Orlando, FL, USA; October 2003*]. The aim of this study was to determine the effect of temsirolimus on lymphocyte proliferation and cytokine production. Since lymphocytes and cytokines are significantly involved in the pathogenesis of rheumatoid arthritis, temsirolimus could have

disease-modifying antirheumatic drug (DMARD) activity against rheumatoid arthritis via the inhibition of these factors.[3]

According to Wyeth's investor presentation in June 2004, the patent covering temsirolimus is due for expiry in 2014.

Table I. Features and properties

Chemical name	[1*R*,9*S*,12*S*[1" *R*,3" *R*,4" *R*],15*R*,18*R*,19*R*,21*R*,23*S*,30*S*,32*S*,35*R*]-1,18-Dihydroxy-12-[2-[4-[3-hydroxy-2-(hy(cyclohexyl]-1-methylethyl]-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-d [30.3.1.0(4,9)]hexatriaconta-16(*E*),24(*E*),26(*E*),28(*E*)-tetraene-2,3,10,14,20-pentaone
Molecular formula	C56 H87 N O16
CAS number	162635-04-3
WHO ATC code	L04A-A (Selective immunosuppressive agents) M01 (Antiinflammatory and Antirheumatic Products) L01D-C (Other cytotoxic antibiotics) N07X (Other Nervous System Drugs)
EphMRA ATC code	M1A (Anti-Rheumatics, Non-Steroidal) N7 (Other CNS Drugs) L1D (Antineoplastic Antibiotics) L4A (Immunosuppressive Agents)
Originator	Wyeth: USA
Highest development phase	Phase II (USA)
Properties	
Mechanism of action	Interferon γ antagonists
Pharmacodynamics	Cytotoxicity in human brain tumour cell lines; tumour growth delay in medulloblastoma and glioblastoma xenografts; reversibly inhibits lymphocyte activation and cytokine production *in vitro*
Route	IV-infusion
Adverse events	Most Frequent: Drug hypersensitivity, Mucositis, Skin disorders; Occasional: Asthenia, Pruritus; Rare: Diarrhoea, Hypocalcaemia, Vomiting

1. Profile

1.1 Pharmacokinetics

Temsirolimus' pharmacokinetic parameters following weekly treatment have been examined in various studies including a phase I dose-escalation study among 24 patients with cancer at doses from 7.5 to 220 mg/m^2 and among 16 patients with advanced renal cancer in doses of 25, 75 and 250mg. With increasing dose (25 to 250 mg/m^2), temsirolimus exposure in whole blood increased with C_{max} ranging from 595 to 2830 ng/mL and AUC from 1580 to 2700 ng • h/mL. Temsirolimus distribution exceeded total body water and increased with dose, while Vd_{ss} ranged from 232 to 897L. CL of temsirolimus also increased with dose from 16.1 to 98.0 L/h. Sirolimus, a major metabolite of temsirolimus, exhibited exposures typically exceeding that of the parent drug. Mean $t_{1/2}$ for temsirolimus was 13h and for sirolimus this ranged from 40 to 57h. Data from dose escalation indicated that no advantage in exposure or its variability was gained by using body surface area-normalised dosing, therefore flat dosing was adopted for further clinical development. In addition, no age or gender differences in exposure have been observed to date.[4,5]

Among the 45 patients with solid tumours receiving temsirolimus 0.75–19.1 mg/m^2/day by IV infu-

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