Genvir Flamel Technologies

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Flamel Technologies is developing Genvir (formerly known as Viropump), a twice-daily controlled-release formulation of aciclovir, for potential use in the treatment of herpes simplex virus and varicella zoster virus infections. Genvir utilizes Flamel's proprietary Micropump technology, a microparticle-based drug delivery system designed to extend the time of absorption of drugs in the small intestine. The drug shows a comparable therapeutic efficacy to valaciclovir and famciclovir (both GlaxoSmithKline) [313393]. Phase III trials have been completed [302829]. In August 2000, Flamel filed for regulatory approval for the treatment of herpes in France, as a prelude to a pan-European approval [378641] and is preparing an IND application to begin clinical trials for genital herpes in the US [245970].

Originator Flamel Technologies SA

Status Pre-registration

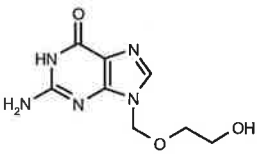
Indication Herpes simplex virus infection, Varicella-zoster virus infection

Action DNA polymerase inhibitor, thymidine kinase inhibitor

Biotechnology Controlled release formulation, oral

Synonyms Flamel, Viropump

CAS 6*H*-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-
Registry No: 59277-89-3



Introduction

Genvir (Viropump) is a twice-daily controlled-release formulation of aciclovir, which employs Micropump technology developed by Flamel Technologies SA, that is expected to receive pan-European approval in the near future [378641], [403279]. Micropump is a microparticle technology containing a high number of unit doses designed for controlled-release and taste-masking applications [378641]. The technology allows sustained drug release in the small intestine over an extended period of time without dependence on the colon for adsorption.

It is hoped that this technology will overcome the short half-life in plasma characteristic of oral aciclovir [403268]. In addition, it is envisioned that this new delivery mechanism will enhance patient compliance because of less frequent dosing and overcome the lack of therapeutic coverage during the night-time hours.

Pharmacology

No data are available on animal studies with Genvir. A set of experiments demonstrated that the micropump technology increased the short half-life of aciclovir in plasma from 2.5 h to 6 to 7 h [403268], [403272].

Metabolism

The half-life of aciclovir in human plasma was increased from 2.5 h to 6 to 7 h by using the Micropump release system [403268], [403272].

Toxicity

No data are currently available.

Clinical Development

Phase I

No data are currently available.

Phase II

No data are currently available.

Phase III

A phase III multinational and multicenter, double-blind study in France and Germany evaluated 419 patients with acute genital herpes episodes. Twice-daily administration of Genvir, each dose containing 600 mg aciclovir, was evaluated for efficacy in parallel with Zovirax (GlaxoSmithKline) given five times daily, with each dose containing 200 mg aciclovir [237755], [319664]. Half the patients received Genvir and the other half received Zovirax. After 5 days of treatment with Genvir, 53.6% of patients had healed lesions, compared with 45.75% of patients receiving Zovirax [403278]. The aborted episode rate was 7.2 and 6.1% for Genvir and Zovirax, respectively. The data also suggested that Genvir was efficacious and reduced the rate of appearance of new lesions [311525], [313393].

An additional trial in 596 patients, comparing Genvir (600 mg bid) to Zovirax (200 mg five times daily) showed that Genvir was as effective as Zovirax [320660]. When tested in parallel with other therapies such as valaciclovir (GlaxoSmithKline) and famciclovir (SmithKline Beecham plc), Genvir was comparably effective [313393].

Side Effects and Contraindications

No adverse reactions have been reported for Genvir relative to placebo controls or Zovirax treatment [319664]. No contraindications have been indicated [403268].

Current Opinion

To date there is a paucity of peer-reviewed, published information on the efficacy of Genvir. However, data from phase III clinical trials in Europe support the notion that this mode of delivery is every bit as efficacious as the traditional

dosing regimen of aciclovir because it apparently increases the half-life in plasma. The Micropump technology used for delivering the aciclovir in a sustained-release fashion makes this form extremely advantageous because it only has to be administered twice daily. This is expected to dramatically increase patient compliance. There are also anecdotal reports that Genvir is as efficacious as valaciclovir, the orally bioavailable form of aciclovir, for treating mucocutaneous herpes infections. To date, there have been no data published from phase III clinical trials in the US. However, Flamel Technologies SA announced the filing of Genvir in August 2000 [378641]. The filing in France is expected to ultimately result in pan-European approval of the product. Nevertheless, until reports on the outcome of phase III clinical trials in Europe and the US have been published, it would be premature to forecast the future of this drug delivery system in a clinical situation.

Development history

Developer	Country	Status	Indication	Date	Reference
Flamel Technologies SA	France	PR	Herpes simplex virus infection	16-AUG-00	378641
Flamel Technologies SA	France	C3	Herpes Simplex virus infection	12-MAR-97	237755
Flamel Technologies SA	France	DR	Varicella zoster virus infection	12-MAR-97	237755

Literature classifications

Metabolism

Study Type	Effect Studied	Experimental model	Results	Reference
In vitro	Pharmacokinetics.	Human plasma.	Half-life in human plasma is increased to 6 to 7 h.	403268 403272

Clinical

Effect studied	Experimental model	Results	Reference
Phase III. Episodic treatment of genital herpes lesions.	Double-blind study in 419 patients with recurrent genital herpes receiving Genvir (600 mg bid) or Zovirax (200 mg five times daily).	Genvir was as effective as Zovirax in reducing lesions.	319664
Phase III. Lesion healing.	Double-blind study in 419 patients with recurrent genital herpes receiving Genvir (600 mg bid) or Zovirax (200 mg five times daily).	Healed lesions were observed in 53.6% of patients treated with Genvir and 45.7% of patients treated with Zovirax.	403278
Phase III. Aborted episode rate.	Double-blind study in 419 patients with recurrent genital herpes receiving Genvir (600 mg bid) or Zovirax (200 mg five times daily).	The aborted episode rate was 7.2 and 6.1%.	313393
Phase III. Efficacy.	Double-blind study in 596 patients receiving either Genvir (600 mg bid) or Zovirax (200 mg five times daily).	Genvir was as effective as Zovirax.	320660

Associated patent

Title Oral pharmaceutical and/or nutritional microcapsules comprising polymer coating.

Assignee Flamel Technologies SA

Publication EP-00709087 01-MAY-96

Priority FR-00012759 18-OCT-94

Inventors Autant P, Selles J-P, Soula G.

Associated references

237755 **Flamel commences phase III clinical trial of controlled-release aciclovir for treatment of genital herpes.** Flamel Technologies *PRESS RELEASE* 1997 January 30

245970 **Flamel Technologies SA reports first quarter 1997 results.** Flamel Technologies *PRESS RELEASE* 1997 May 12

302829 **Flamel Technologies announce clinical trial completion for genvir and progress with asacard.** Flamel Technologies *PRESS RELEASE* October 27

311525 **Flamel reports revenue rise plans launch of first product.** *BIOWORLD INTERNATIONAL* 1998 **3** 44 6

313393 **Flamel's Genvir for herpes shows strong phase III data.** *BIOWORLD INTERNATIONAL* 1998 **3** 45 1-5
• *Reports the reduced rate of appearance of new herpes lesions following Genvir treatment.*

319664 **Genvir, a sustained-release formulation of acyclovir given twice-daily, is at least equivalent to Zovirax, given five times daily for the episodic treatment of recurrent genital herpes.** Joly P, Fuder H, Vivet P, Soula G *ANTIVIRAL RES* 1999 **41** 2 Abs 85
• *An abstract from a scientific meeting describing the results of a second phase III clinical trial treating recurrent genital herpes infections.*

320660 **International Society for Antiviral Research - 12th International Conference (Part VIII), Jerusalem, Israel.** Field H *IDDB MEETING REPORT* 1999 March 21-25

378641 **Flamel announces filing of Genvir, a twice daily controlled release acyclovir for herpes treatment.** Flamel Technologies SA *PRESS RELEASE* 2000 August 10

403268 **Genvir, controlled release aciclovir. Flamel Technologies SA Fact Sheet 2000.** Flamel Technologies SA *COMPANY WORLD WIDE WEB SITE* 2001 March 28
• *Reports the increased plasma half-life of aciclovir in the Genvir formulation.*

403272 **Current recommendations for the treatment of genital herpes.** Leung DT, Sacks SL *DRUGS* 2000 **60** 6 1329-1352
• *Reports on increased plasma half-life of aciclovir in the Genvir formulation. It is part of a review comparing genital herpes treatments.*

403278 **Phase III data released for herpes drug.** *DERMATOL TIMES* 1998 December
• *Gives efficacy statistics on a phase III genital herpes clinical trial in France and Germany.*

403279 **Aciclovir-Genvir-Zovirax-AntiHSV.** Anon *DRUGS FUTURE* 2000 **25** 11 1173-1174
• *Reports on Flamel Technologies filing for approval of Genvir.*