**Genvir** Flamel Technologies
Dale L Barnard

**Address**
Utah State University
Institute for Antiviral Research
5800 Old Main Hill
Logan
UT 84322-5600
USA
Email: honery@cc.usu.edu

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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].

**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.

**Originator** Flamel Technologies SA

**Status** Pre-registration

**Indication** Herpes simplex virus infection, Varicella-zoster virus infection

**Action** DNA polymerase inhibitor, thymidine kinase inhibitor

**Biototechnology** Controlled release formulation, oral

**Synonyms** Flamel, Viropump

**CAS 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]—

**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 [237785], [519664]. 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.

<table>
<thead>
<tr>
<th>Developer</th>
<th>Country</th>
<th>Status</th>
<th>Indication</th>
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<th>Reference</th>
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<td>Flamel Technologies SA</td>
<td>France</td>
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<td>378641</td>
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<td>Flamel Technologies SA</td>
<td>France</td>
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<td>Varicella zoster virus infection</td>
<td>12-MAR-97</td>
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<thead>
<tr>
<th>Study Type</th>
<th>Effect Studied</th>
<th>Experimental model</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vitro</td>
<td>Pharmacokinetics</td>
<td>Human plasma.</td>
<td>Half-life in human plasma is increased to 6 to 7 h.</td>
<td>403268, 403272</td>
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</table>

**Clinical**

<table>
<thead>
<tr>
<th>Effect studied</th>
<th>Experimental model</th>
<th>Results</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Phase III. Episodic treatment of genital herpes lesions.</td>
<td>Double-blind study in 419 patients with recurrent genital herpes receiving Genvir (600 mg bid) or Zovirax (200 mg five times daily).</td>
<td>Genvir was as effective as Zovirax in reducing lesions.</td>
<td>319664</td>
</tr>
<tr>
<td>Phase III. Lesion healing.</td>
<td>Double-blind study in 419 patients with recurrent genital herpes receiving Genvir (600 mg bid) or Zovirax (200 mg five times daily).</td>
<td>Healed lesions were observed in 53.6% of patients treated with Genvir and 45.7% of patients treated with Zovirax.</td>
<td>403278</td>
</tr>
<tr>
<td>Phase III. Aborted episode rate.</td>
<td>Double-blind study in 419 patients with recurrent genital herpes receiving Genvir (600 mg bid) or Zovirax (200 mg five times daily).</td>
<td>The aborted episode rate was 7.2 and 8.9%.</td>
<td>313393</td>
</tr>
<tr>
<td>Phase III. Efficacy.</td>
<td>Double-blind study in 596 patients receiving either Genvir (600 mg bid) or Zovirax (200 mg five times daily).</td>
<td>Genvir was as effective as Zovirax.</td>
<td>320660</td>
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**Associated patent**

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

**Assignee** Flamel Technologies SA

**Publication** EP-00790037 01-MAY-96

**Priority** FR-00012759 18-OCT-94

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

**Associated references**

319664 Genvir, a sustained-release formulation of aciclovir given twice-daily, is at least equivalent to Zovirax, given five times daily for the episodic treatment of recurrent genital herpes. Joly P, Fudor H, Vivet P, Soula G ANTIVIRAL RES 1999 41 2 Abe 85

- An abstract from a scientific meeting describing the results of a second phase III clinical trial treating recurrent genital herpes infections.

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


- 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 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.

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- Gives efficacy statistics on a phase III genital herpes clinical trial in France and Germany.

432379 Aciclovir-Genvir-Zovirax-AntiHSV. Anon DRUGS FUTURE 2000 25 11 1173-1174

- Reports on Flamel Technologies filing for approval of Genvir.