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ADISINSIGHT REPORT

Elsulfavirine: First Global Approval

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Abstract Elsulfavirine (Elpida®) is a new-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) being developed by Viriom for the treatment and prevention of human immunodeficiency virus (HIV) infections. It is the prodrug of the active compound VM-1500A, a small molecule selective NNRTI, which prevents HIV replication. In June 2017, elsulfavirine received its first global approval in Russia for the treatment of HIV-1 infections in combination with other antiretroviral medicines. Other formulations of this drug are also being evaluated in pre-clinical and phase II studies for the treatment of HIV infections and/or pre-exposure and post-exposure prophylaxis. This article summarizes the milestones in the development of elsulfavirine leading to this first approval in HIV-1 treatment.

1 Introduction

Elsulfavirine (Elpida®) is a new-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) being developed by Viriom for the treatment and prevention of human immunodeficiency virus (HIV) infections [1]. Elsulfavirine is the prodrug of the active compound VM-1500A, a small molecule selective NNRTI (Sect. 2.1) [1]. Available anti-HIV drugs interfere with various phases of the virus life-cycle to inhibit its proliferation, and are used in combination therapy (with ≥ 2 drugs) to reduce the viral load below the detectable limit [2]. Most available treatment regimens have comparable efficacy; however, challenges associated with toxicity, tolerability, interactions, viral resistance and cross-resistance to the drugs [3], highlight the need for continuous research and development of new treatment options.

An oral formulation of elsulfavirine has been approved in Russia for the treatment of HIV-1 infections with other antiretroviral medicines (based on results of a 48-week trial; Sects. 2.3, 2.4) [1]; the recommended dosage is 20 mg once daily, taken 15 min before meals [4]. Phase II development of a sustained-release oral formulation of elsulfavirine is underway for the treatment of HIV infections and/or pre-exposure prophylaxis and post-exposure prophylaxis [5]. Preclinical development of a fixed-dose combination of elsulfavirine with a nucleoside regimen is also underway; long-acting injectable formulations of the parent drug (VM-1500A) are in preclinical development for the treatment of HIV infections, pre- and post-exposure prophylaxis [5]. A topical (gel) formulation of elsulfavirine was in pre-clinical development for the prevention of HIV infections; however, development of this formulation in this indication has been discontinued.

1.1 Company Agreements

In May 2016, Viriom raised equity and non-equity financing, including a three-year grant from the Skolkovo Foundation, for the development of fixed-dose combinations and long-acting injection formulations of elsulfavirine [6].

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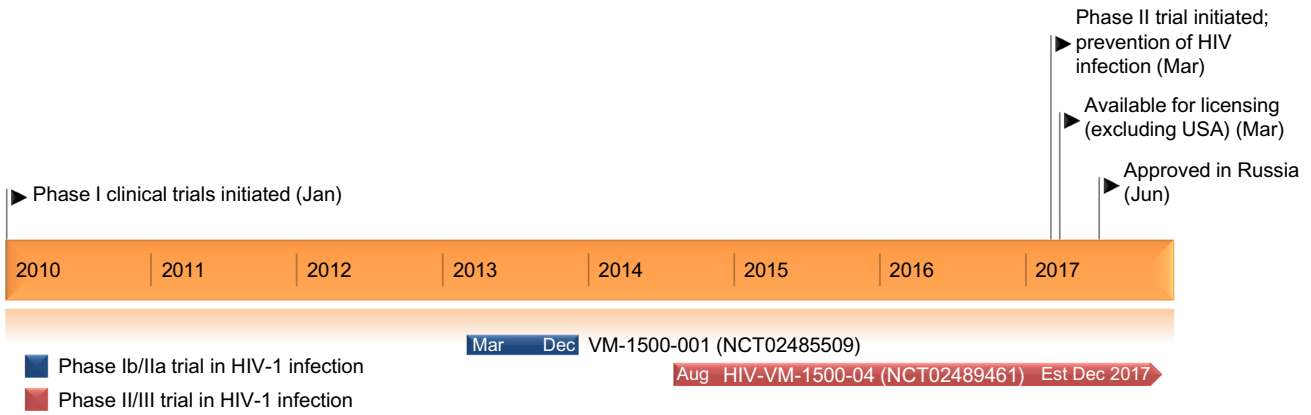


Key milestones in the development of elsulfavirine. *HIV-1* human immunodeficiency virus-1

As of July 2015, Viriom has intellectual property protection for the composition, formulations and methods for elsulfavirine in all major and global markets. In November 2013, Viriom signed a global expansion of its commercial rights to elsulfavirine to include all therapeutic indications and drug combinations [7]; Viriom entered into a licensing agreement with Roche in October 2009, for the development and commercialization of potential drug candidates against HIV infections [8]. In October 2009, Viriom selected Chemical Diversity Research Institute (a wholly owned subsidiary of ChemDiv, Inc.) as a service partner to develop innovative HIV compounds; the programme including pre-clinical and clinical studies was expected to start in 2010 [9]. The preclinical candidates belonging to the NNRTI drug class were to be provided by Roche, who will also receive royalties from the resulting sales in Russia, Ukraine, Belarus and Kazakhstan, and retain their rights in all other territories. Viriom will be receiving license fees, development milestones and royalties on worldwide sales.

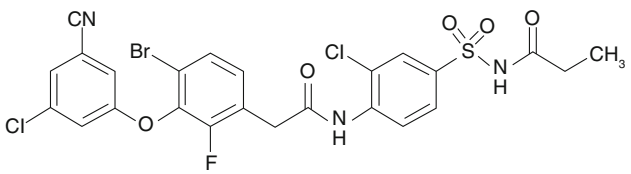
2 Scientific Summary

2.1 Pharmacodynamics

Elsulfavirine is an NNRTI, and is the prodrug for the potent and highly selective active compound VM-1500A [10–12]. Reverse transcriptase, an HIV enzyme, is released and used by the HIV to convert its RNA into HIV DNA inside the CD4 cells, and allows the HIV to enter the CD4 nucleus and combine with the cell's DNA [2]. VM-1500A acts to inhibit reverse transcriptase, thereby preventing HIV replication. The antiviral activity of elsulfavirine is broad, with activity demonstrated towards various viral strains and clinical isolates of HIV, including those resistant to other NNRTIs (presentation) [13]. Furthermore, elsulfavirine was associated with a low probability of cross resistance or resistance development, and a high genetic barrier to the development of resistant drug mutations [1, 13].

2.2 Pharmacokinetics

Following once daily oral administration of elsulfavirine (20 or 40 mg) or placebo in HIV-infected patients for 7 days in a phase I/II trial (VM-1500-001; NCT02485509), the pharmacokinetic profile supported once daily dosing of elsulfavirine with neither dose showing superiority (abstract plus poster) [14]. In the second part of the trial, HIV-infected patients were randomized (7:1) to receive once daily doses of elsulfavirine 20 mg or placebo (cohort 1), or elsulfavirine 40 mg or placebo (cohort 2) for 7 days. On day 1 in HIV-infected patients, the mean half-life ($t_{1/2}$) of elsulfavirine following oral administration of the 20 mg dose was 1.9 h and for elsulfavirine 40 mg was 2.1 h; on day 7, the mean $t_{1/2}$ of elsulfavirine following administration of the 40 mg oral dose was 2.4 h [14]. After 7 days, the mean $t_{1/2}$ of the active metabolite (VM-1500A) was 7.4 and 5.4 days for the elsulfavirine 20 and 40 mg doses.



Chemical structure of elsulfavirine

The mean time to reach maximum elsulfavirine plasma concentration (t_{max}) was 0.9 h in elsulfavirine 20 mg recipients (on day 1) and 1.0 and 1.1 h in elsulfavirine 40 mg recipients (on days 1 and 7); mean t_{max} values for VM-1500A were 6.3 and 6.2 days after dosing with elsulfavirine 20 and 40 mg for 7 days [14]. Dose-dependent increases in exposure to elsulfavirine and its metabolite were evident following the administration of elsulfavirine 20 and 40 mg in HIV-infected patients [14]. Based on these pharmacokinetic findings, further development of elsulfavirine was warranted.

A pre-clinical pharmacokinetics study of 10 mg/kg injectable (subcutaneous or intramuscular) elsulfavirine or VM-1500A in beagle dogs provided a proof of concept that the parent drug (VM-1500A) could be developed into long-acting injectable formulations (abstract plus poster) [15]; further pre-clinical development is warranted (Sect. 2.5).

Concomitant administration with substrates of CYP3A4 and CYP2B6 (e.g. amitriptyline, atorvastatin, clarithromycin, citalopram, ketoconazole) can result in clinically significant reductions in the concentrations and effects of these agents [4].

2.3 Therapeutic Trials

The efficacy of elsulfavirine has been evaluated in the international, multicentre, randomized, partially blind phase II/III clinical trial (HIV-VM1500-04; NCT02489461) [abstracts plus posters] [11, 16]. The dose-finding stage of this trial (stage 1) evaluated the efficacy of once daily elsulfavirine (20 or 40 mg) versus efavirenz, both in combination with tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), at 12 weeks, with the results of this stage of the trial supporting the selection of elsulfavirine 20 mg for further study. This was followed by stage 2 of the study, which evaluated the efficacy [and safety (Sect. 2.4)] of elsulfavirine 20 mg compared with efavirenz, both in combination with TDF/FTC, at 48 weeks.

In the dose-finding study in patients with HIV infection who are ART-naive (stage 1), median HIV-1 RNA levels decreased from a baseline value of 4.7 to 1.8 $\log_{10}$ copies/mL at 12 weeks in the elsulfavirine 20 mg group ($n = 30$) [interim analysis]; decreases in HIV-1 RNA levels from baseline were also evident at week 12 in the elsulfavirine

Features and properties of elsulfavirine

Alternative names	Elpida; elpivirine; R1206; RO 4970335; RO 5011500; VM 1500; VM 1500 LAI; VM 1500 Long acting injectable
Class	Acetamides; Antivirals; Nitriles; Small molecules; Sulfones
Mechanism of action	Non-nucleoside reverse transcriptase inhibitor
Route of administration	Oral (approved), parenteral (in development), topical (discontinued)
Pharmacodynamics	Acts as a prodrug for the potent and highly selective active compound VM-1500A; inhibits reverse transcriptase, which results in prevention of HIV replication
Pharmacokinetics	Elsulfavirine: mean $t_{1/2}$ 1.9 h, mean t_{max} 0.9 h; VM-1500A: mean $t_{1/2}$ 7.4 days, mean t_{max} 6.3 days
Adverse events	
Most frequent ($\geq$ 5%)	Dizziness, headache, sleep disorders, nausea, diarrhoea
Occasional ($<$ 5%)	Unusual dreams, memory loss, apathy, depression, fatigue
Rare ($<$ 1%)	Skin rash
ATC codes	
WHO ATC code	J05A-G (Non-nucleoside reverse transcriptase inhibitors)
EphMRA ATC code	J5C3 (Non-nucleoside reverse transcriptase inhibitors)
Chemical Name	N-(4-{2-[4-bromo-3-(3-chloro-5-cyanophenoxy)-2-fluorophenyl]acetamido}-3-chlorobenzenesulfonyl)propanamide

$t_{1/2}$ half-life, t_{max} time to maximum plasma concentrations

40 mg ($n = 29$) [from 4.9 to 1.7 $\log_{10}$ copies/mL] and efavirenz 600 mg ($n = 28$) [from 4.6 to 1.7 $\log_{10}$ copies/mL] groups (poster) [10].

Elsulfavirine 20 and 40 mg demonstrated superiority to efavirenz by 11.8 and 4.7% in terms of the effectiveness to reduce the level of viral load to < 400 copies/mL after 12 weeks of therapy, and a respective lower limit of 95% confidence interval of −2.6 and −11.5% which fall to the right of the non-inferiority margin of −15%; therefore non-inferiority of elsulfavirine (both doses) was demonstrated [10]. There were no significant differences between recipients of elsulfavirine (20 or 40 mg) or efavirenz in terms of the reduction of median HIV RNA content after 12 weeks of therapy depending on baseline viral load (i.e. ≥ 100,000 or < 100,000 copies/mL). After 12 weeks of treatment with elsulfavirine 20 and 40 mg and efavirenz, HIV-1 RNA levels of < 400 copies/mL were achieved in 93.3, 86.2 and 81.5% of each group, respectively [modified intent-to-treat (mITT) analysis] [10]. These findings were supported by the per protocol analysis.

After 12 weeks of therapy, median CD4+ lymphocyte levels increased from baseline in all treatment groups, although the average increases from baseline were only significant for the elsulfavirine 20 mg ($p < 0.001$) and efavirenz ($p < 0.05$) treatment groups [10]. Furthermore, an increase in the median immunoregulatory index (i.e. CD4/CD8+ lymphocyte ratio) from baseline (0.357–0.378) was evident for all treatment groups after 12 weeks of treatment (0.487–0.522); however, a significant ($p < 0.001$) reduction in the average number of CD8+ lymphocytes was only evident in the elsulfavirine 20 mg group [10].

At week 48, significantly ($p < 0.05$) more antiretroviral therapy (ART)-naive, HIV-1 infected patients in the elsulfavirine 20 mg group ($n = 60$) than in the efavirenz 600 mg ($n = 58$) group completed treatment (91.7 vs. 78.3%) [abstract plus poster] [11]. Of those who completed treatment at week 48 in the mITT analysis, all patients in both groups had HIV-1 RNA levels of < 400 copies/mL and 81.0 and 73.7% of patients in the elsulfavirine and efavirenz groups had HIV RNA of < 50 copies/mL; median HIV RNA levels at baseline were 4.7–4.8 $\log_{10}$ copies/mL across groups. Significantly ($p < 0.05$) more elsulfavirine recipients had HIV RNA levels of < 50 copies/mL (84.5 vs. 66.7% for efavirenz recipients) at week 24 [16]. Furthermore, the majority of patients with high baseline HIV-1 RNA levels (> 100,000 copies/mL) in the elsulfavirine ($n = 18$) and efavirenz ($n = 22$) groups also had HIV RNA levels of < 50 copies/mL (77.8 vs. 68.2%) at week 48 [11]. There were no patients in either group with virological failure (i.e. two consecutive HIV RNA plasma levels of > 400 copies/mL).

The CD4+ lymphocyte counts increased by 179 and 182 cells/mm^3 in recipients of elsulfavirine- and efavirenz-based therapy for 48 weeks, with an increase in the median CD4/CD8+ ratio by 0.37 (to 0.78) and 0.29 (to 0.63), respectively [11]. At baseline, median CD4+ T lymphocyte counts were 349 and 379 cells/mm^3 in the elsulfavirine and efavirenz groups.

In a phase IIa trial (VM-1500-001; NCT02485509) in patients with HIV infection who are ART-naive with HIV-1 RNA levels of > 5000 copies/ml and CD4 counts of > 250 cells/mm^3, patients were randomized to receive 7 days of treatment with elsulfavirine 20 mg ($n = 7$) or placebo ($n = 1$) [cohort 1], and eight patients were randomized to receive 7 days treatment with elsulfavirine 40 mg ($n = 7$) or placebo ($n = 1$) [cohort 2] (abstract) [17]. Elsulfavirine demonstrated excellent antiviral activity with a 1.8 $\log_{10}$ reduction in HIV-1 RNA, thus indicating that it is a good once daily candidate for the treatment of HIV infections [17]. At day 8, average HIV-1 RNA levels decreased from 82,499 (day 1) to 2133 copies/mL in the elsulfavirine 20 mg group and from 303,000 to 248,000 copies/mL with placebo (cohort 1); average HIV-1 RNA levels decreased from 93,671 copies/mL at day 1 to 1316 copies/mL at day 8 in the elsulfavirine 40 mg group and from 126,000 to 116,206 copies/mL with placebo (cohort 2) [17]. Furthermore, in recipients of elsulfavirine 20 mg, the average CD4 counts increased from 551 to 592 cells/mm^3 from day 1 to day 8 (vs. from 492 to 517 cells/mm^3 from day 1 to day 8 with placebo), and from 471 to 525 cells/mm^3 in recipients of elsulfavirine 40 mg (vs. from 424 to 388 cells/mm^3 from day 1 to day 8 with placebo) [17].

Key clinical trials of elsulfavirine (Viriom)

Drug(s)	Indication	Phase	Status	Location(s)	Identifier
Elsulfavirine +TDF/FTC, efavirenz +TDF/FTC	Treatment of HIV-1 infections (1st line therapy)	II/III	Ongoing	Russia	HIV-VM1500-04; NCT02489461
Elsulfavirine, placebo	Safety and PK in healthy volunteers and in patients with HIV-1 infections	I/II	Completed	Thailand	VM-1500-001; NCT02485509
Elsulfavirine	PK and safety in healthy volunteers	I	Completed	Russia	01/HIV/2010
Elsulfavirine, darunavir, raltegravir, ritonavir	Drug interaction study in healthy volunteers	I	Completed	Thailand	VM1500-002; NCT02489487
Elsulfavirine, placebo	Safety and PK in healthy volunteers	I	Completed	Russia	02/HIV/2010; NCT02489435

HIV-1 human immunodeficiency virus-1, *pk* pharmacokinetics, *TDF/FTC* tenofovir disoproxil fumarate/emtricitabine

2.4 Adverse Events

Available clinical data [10, 11, 17] indicate that elsulfavirine 20 mg once daily (approved dosage), plus TDF/FTC [11], is generally well tolerated in ART-naive HIV-1 infected patients.

The Russian prescribing information states that the probability of significant adverse events (AEs) occurring very frequently ($\geq$ 10%) or frequently ($\geq$ 1 to $<$ 10%) in recipients of elsulfavirine is low, and that these AEs most commonly occur within the first four weeks of treatment and will resolve without the need to withdraw treatment [4]. These AEs include headache, herpes simplex, leukopenia, neutropenia, sleep disorders, dizziness, vivid dreams, drowsiness, nausea, diarrhoea, dry mouth, vomiting, skin rash, itching, mild proteinuria, polyuria, asthenia, weakness, decreased appetite and fever.

In ART-naive, HIV-1 infected patients, elsulfavirine-based therapy ($n = 60$) was better tolerated than efavirenz-based therapy ($n = 58$) at 48 weeks, with AEs [any grade] being reported by 78.3 and 86.2% of patients in these treatment groups (stage 2 of HIV-VM1500-04; NCT02489461); discontinuations of elsulfavirine or efavirenz were reported in 8.3 and 22.4% of patients, although discontinuation because of an AE related to treatment was only reported in 1.7 and 12.1% of patients in each group [11]. Grade 3–4 AEs were reported in 5.0 and 12.1% of patients in the elsulfavirine and efavirenz groups; in the elsulfavirine group, all grade 3–4 AEs were not drug-related, whereas the majority ($>$ 70%) of grade 3–4 events in the efavirenz group were probably treatment-related [11]. Significantly fewer recipients of elsulfavirine- than efavirenz-based therapy reported AEs that are probably and possibly drug-related (36.7 vs. 77.8%; $p < 0.0001$) [11]. The most frequent AEs (excluding those of special interest) reported in $>$ 5% of patients in any group include diarrhoea (6.7% of elsulfavirine recipients vs. 5.2% of efavirenz recipients), nausea (5.0 vs. 10.3%) and fatigue (3.3 vs. 8.6%).

Significantly fewer recipients of elsulfavirine- than efavirenz-based therapy reported frequent (defined as $>$ 5%) AEs of special interest [central nervous system (CNS) disorders, skin disorders] (31.7 vs. 62.1%; $p < 0.01$) [11]. Dizziness, headache and sleep disorders were reported in 6.7, 15.0 and 5.0% of patients receiving elsulfavirine-based therapy (vs. 27.6, 24.1 and 20.7% of patients receiving efavirenz-based therapy); other CNS AEs reported in $>$ 5% of patients in any group include unusual dreams (3.3 vs. 17.2% of patients in the elsulfavirine and efavirenz groups), insomnia (1.7 vs. 8.6%), memory loss (1.7 vs. 5.2%), sleepiness (3.3 vs. 15.5%), apathy (1.7 vs. 5.2%) and depression (3.3 vs. 12.1%) [11]. There were no occurrences of skin rash in the elsulfavirine group (vs. 22.4% of patients in the efavirenz treatment group).

2.5 Ongoing Clinical Trials

Trials are underway to investigate the use of an oral, once weekly, sustained release formulation of elsulfavirine for the prevention and/or treatment of HIV infections (phase II), and a long-acting injectable formulation of the active metabolite of elsulfavirine (VM-1500A) is in preclinical development for the prevention and/or treatment of HIV infections [5, 13]. Viriom is also developing a fixed-dose combination of elsulfavirine with two NRTIs (emtricitabine, tenofovir disoproxil fumarate) for once-daily oral administration (preclinical development) [13]. The innovative scheme of sequential therapy, where the fixed-dose oral combination is used until the viral load is reduced to undetectable levels, before switching to the once-monthly injectable (intramuscular or subcutaneous) formulation will be presented for the first time as an alternative to life-long intake of drugs.

3 Current Status

Elsulfavirine received its first global approval on 30 June 2017, in Russia, for the treatment of HIV-1 infections in combination with other antiretroviral medicines.

Compliance with Ethical Standards

Funding The preparation of this review was not supported by any external funding.

Conflicts of interest During the peer review process the manufacturer of the agent under review was offered an opportunity to comment on the article. Changes resulting from any comments received were made by the authors on the basis of scientific completeness and accuracy. Zaina T. Al-Salama is a salaried employee of Adis/Springer, is responsible for the article content and declares no relevant conflicts of interest.

Additional information about this Adis Drug Review can be found at http://www.medengine.com/Redeem/99FBF0607E7A1D54.

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