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Global HIV Infection Drug Market & Pipeline Insight

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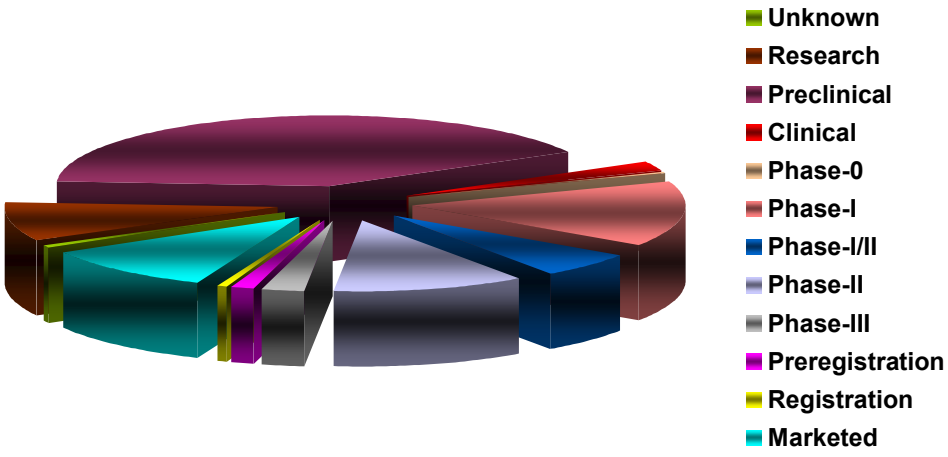
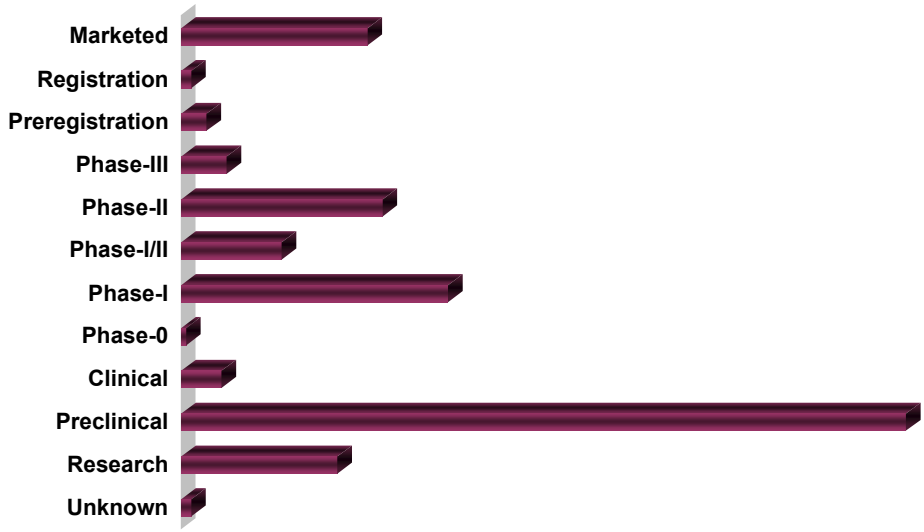


Source: XXXX

Figure 1-7: Global - HIV Infection Drug Pipeline by Phase (Number), 2014



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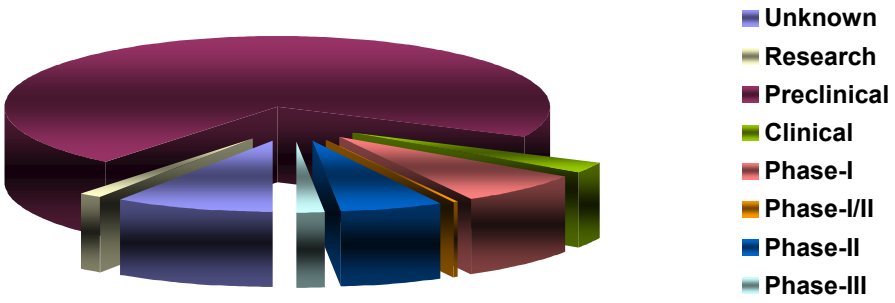

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Figure 1-9: Global - No Development Reported in HIV Infection Drug in Pipeline by Phase (Number), 2014

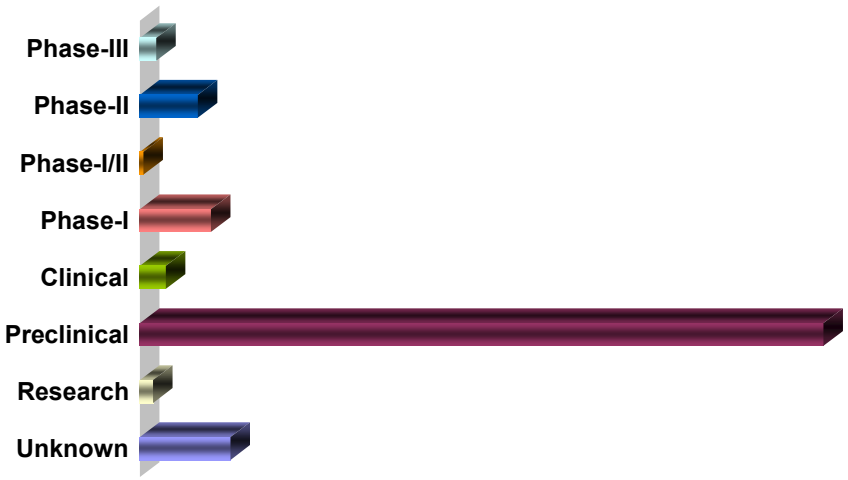

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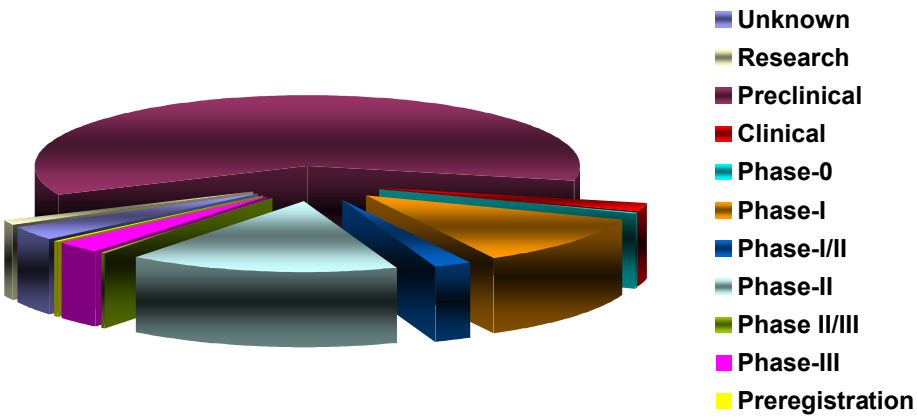
Figure 1-10: Global – Discontinued HIV Infection Drug in Pipeline by Phase (%), 2014

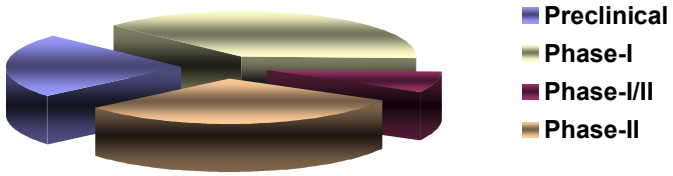


Source: XXXX

Figure 1-11: Global – Discontinued HIV Infection Drug in Pipeline by Phase (Number), 2014

Source: XXXX

Figure 1-12: Global – Suspended HIV Infection Drug in Pipeline by Phase (%), 2014



Source: XXXX

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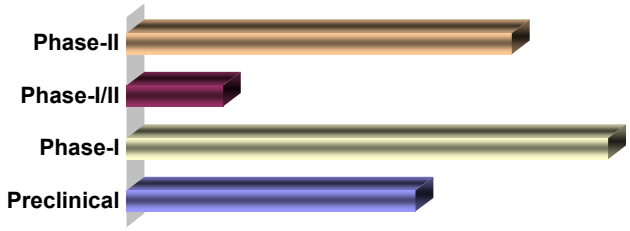

Source: XXXX

3. FDA Regulatory Framework for Development of HIV Vaccine

3.3 HIV Resistance Testing in Antiretroviral Drug Development

This guidance is intended to assist sponsors in the clinical development of drugs for the treatment of human immunodeficiency virus (HIV) infection. Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the role of HIV resistance testing during antiretroviral drug development and marketing and serves as a focus for continued discussion among the Division of Antiviral Products (DAVP), pharmaceutical sponsors, the academic community, and the public. The goal of this guidance is to stimulate the generation of more complete resistance data and analyses for antiretroviral drug products.

This guidance uses a broad definition of the term drugs including, but not limited to, small chemical entities, biologics, monoclonal antibodies, synthetic oligonucleotides, and siRNA, and focuses on resistance to antiretroviral agents as manifested by mutations in the HIV viral genome that result in reduced phenotypic susceptibility to a given drug product. Although mechanisms of cellular resistance to antiretrovirals exist, a discussion of these mechanisms is beyond the scope of this guidance. In addition, loss of susceptibility to drugs is highlighted, rather than hypersusceptibility. However, we acknowledge the potential for results to show increased susceptibility of the virus to one or more antiretroviral drugs and we encourage sponsors to report such observations to the FDA.

Although this guidance focuses on characterization of resistance and cross-resistance during drug development, we recommend application of these principles to currently marketed antiretroviral agents; therefore, we recommend ongoing resistance testing in the postmarketing setting.

This guidance does not imply one type of resistance testing is more useful than another type of resistance testing in the clinical management of HIV infection. This guidance addresses how serial assessments of both genotype and phenotype can be useful in antiretroviral drug development. For characterizing the utility of an antiretroviral drug, both phenotypic and genotypic resistance testing have strengths and limitations as discussed in this guidance.

For information on trial design and endpoints in phase 3 antiretroviral drug development, see the related guidance for industry Antiretroviral Drugs Using Plasma HIV RNA Measurements —
Clinical Considerations for Accelerated and Traditional Approval.

Becaue the field of HIV resistance is evolving, we intend to revise this guidance as new information accumulates. FDA’s guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The primary sources for the recommendations in this guidance are as follows:

• Data analyses and input from the HIV Resistance Collaborative Group (an international, multidisciplinary group consisting of representatives from academic institutions, U.S. and European health regulatory authorities, governmental clinical trial organizations, the pharmaceutical and diagnostics industries, and HIV patient community groups). Data, analyses, and opinions compiled by this group were presented at a 2-day session of the Antiviral Drug Product Advisory Committee, convened November 2-3, 1999, to address issues relating to HIV resistance testing.
• The DAVP's experience with reviewing resistance data for antiretroviral drugs in new drug applications from 1999 to the present, including subsequent analysis and presentation of resistance data to the Antiviral Drug Product Advisory Committee.
• Additional input from pharmaceutical sponsors and the HIV community.

Presentations during the November 1999 advisory committee meeting included the following topics:

• Performance characteristics of genotypic and phenotypic assays
• Prevalence of resistance in antiretroviral naïve patients
• The ability of baseline resistance testing to predict subsequent virologic response
• Clinical factors that might influence the results of resistance testing Summaries of presentations at this meeting have been published in Antiviral Therapy (Richman 2000; Hammer and Pedneault 2000; DeGruttola et al. 2000; Laessig et al. 2000), and the transcripts of the FDA advisory committee can be found on the Internet.

III. HIV RESISTANCE TESTING — GENERAL

Because of its high rate of replication (109 to 1010 virions per person per day) and error-prone polymerase, HIV can easily develop mutations that alter susceptibility to antiretroviral drugs. As a result, the emergence of resistance to one or more antiretroviral drugs is one of the more common reasons for therapeutic failure in the treatment of HIV. In addition, the emergence of resistance to one antiretroviral drug

sometimes confers a reduction in or a loss of susceptibility to other or all drugs of the same class.

The application of laboratory technologies, such as gene amplification, automated nucleic acid sequencing, and nucleic acid hybridization, and the availability of recombinant viruses for testing phenotypic susceptibility have permitted advances in HIV resistance testing. Many clinicians and investigators are currently using these technologies in the clinical management of HIV.

However, performance characteristics (e.g., sensitivity, specificity, and reproducibility) for many of the assays in investigational use have not been fully established. In addition, the clinical significance of many mutations or mutational patterns has not been defined completely for many antiretroviral drugs. Likewise, the quantitative relationship between reductions of cell culture susceptibility and loss of clinical activity has not been established for most drugs. Consequently, many of the current package inserts are deficient in the amount and type of resistance data describing the utility of a drug in the setting of resistance or reduced susceptibility.

Despite limitations of resistance assays and their interpretation, several randomized controlled studies have demonstrated that virologic outcome, at least over the short term, may be improved when genotypic or phenotypic data are used to guide choice of drug regimens in patients with loss of virologic response to prior regimens (Baxter et al. 2000; Cohen et al. 2002; Durant et al. 1999; Melnick et al. 2000; Meynard et al. 2000; Tural et al. 2002). The FDA recommends that characterization of resistance and cross-resistance be a part of antiretroviral drug development so that clinically relevant information is available at the time of approval. An efficient way to accomplish the goal of having clinically relevant information available at the time of approval is to include resistance testing in all phases of drug development. As discussed below, assessment of resistance should not be delayed until phase 3 or post-approval. We recommend that, before or during phase 1 and phase 2 studies, investigators begin assessing the potential of a drug to select resistant viruses and the drug's activity against HIV isolates resistant to other antiretroviral agents. During early development, a wide range of doses should be evaluated and pharmacokinetic data should be collected, providing information to investigate the relationship between drug exposure and resistance

Optimally, a comprehensive evaluation of a new drug's resistance and cross-resistance profile will promote more rational use of antiretroviral drug combinations in the future.

5. Global HIV Infection Drug Clinical Pipeline by Phase, Company & Country

This chapter gives comprehensive insight on 315 HIV drugs in clinical pipeline.

5.3 Preclinical

HIV Drug Profile: Antiviral Agents - ConjuChem

Alternate names	DAC™ HIV; DAC™:HIV; DAC:HIV
Originator	ConjuChem Biotechnologies
Available for licensing	Yes (as at 16/09/2011)
Highest development phase	Preclinical (USA)
Active Development - indications	HIV infections
Class	Peptides
Mechanism of action	Viral fusion protein inhibitors, Virus internalisation inhibitors
- WHO ATC code	J05A (Direct acting antivirals)
- EphMRA ATC code	J5 (Antivirals for Systemic Use)

Owner/Originator/Collaborator/Licensee

Name	Role	Country	Type	Ownership
ConjuChem	Owner	USA	Biotechnology	Private
ConjuChem Biotechnologies	Originator	Canada	Biotechnology	Private

Development Phase

Phase	Indication	Country	Route
Preclinical	HIV infections	USA	Parenteral

Introduction

ConjuChem (formerly ConjuChem Biotechnologies) is developing a series of antiviral agents using its Drug Affinity Complex (DAC™) technology. One target area for drugs in

the control of HIV is to inhibit the entry of the HIV virus into the cell using anti-fusion, anti-entry peptides. One such peptide is C34 which blocks virus-mediated cell-cell fusion and de novo HIV-1 infection of T cells. However, peptides like this have a very short half-life and frequent dosing would be required. ConjuChem has developed a lead compound, DAC™: HIV (or DAC™ HIV), which is a C34 peptide based on DAC™ technology. Preclinical development is in progress in the US.

ConjuChem stated on its website in September 2011 that it was offering the possibility of partnership agreements for its internally developed programmes.

ConjuChem Biotechnologies Inc. of Montreal, Canada, was relaunched in August 2011 as a privately held US company, ConjuChem LLC, based in Los Angeles, California.

ConjuChem signed an agreement granting Trimeris an exclusive right to negotiate terms and conditions of a worldwide licence to ConjuChem's (DAC™) technology. Under the agreement, ConjuChem was to negotiate exclusively with Trimeris for the licensing of DAC™ technology for the prevention and/or treatment of HIV infection. However, this collaboration between the two companies is no longer active; at the conclusion of the feasibility study, both companies decided to allocate and focus the majority of their efforts on their respective lead programmes. ConjuChem continues to conduct research work with their DAC™ technology on several promising antiviral compounds for various indications.

HIV Drug Profile: Antiviral Therapeutics – Aphios

Alternate names	Albasomes™; APP-0303; APP-0401; Betulinic acid - Aphios; Bryostatin -1/histone deacetylase inhibitors; Hypericin - Aphios
Originator	Aphios Corporation
Highest development phase	Preclinical (Spain, USA)
Active Development - indications	HIV infections
Mechanism of action	HIV replication inhibitors, Virus replication inhibitors
- WHO ATC code	J05 (Antivirals for Systemic Use)
- EphMRA ATC code	J5B (Antivirals, excluding anti-HIV products), J5C (HIV antivirals)

Owner/Originator/Collaborator/Licensee

Name	Role	Country	Type	Ownership
Aphios Corporation	Originator	USA	Biopharmaceutical	Private
Aphios Corporation	Owner	USA	Biopharmaceutical	Private
VivaCell Biotechnology Espana	Collaborator	Spain	Biotechnology	Private

Brand Name

Organisation	Country	Indication	Brand Name
Aphios Corporation	USA	HIV infections	Albasomes™

Development Phase

Phase	Indication	Country
Preclinical	HIV infections	Spain
Preclinical	HIV infections	USA

Introduction

Aphios Corporation in the US is developing a variety of antiviral therapeutics that are derived mainly from marine and plant sources. This programme is at the preclinical stage of development for the treatment of HIV infections and at the discovery stage for the treatment of smallpox.

Aphios has established a unique library of diverse marine micro-organisms and marine molecule fractions for the rapid discovery and development of anti-infective compounds. In addition, Aphios has modified light-mediated viral inactivation compounds, such as hypericin from St John's wort, to make such compounds useful as therapeutic tools. The light-sensitive compounds are coupled with chemiluminescence generated by native enzymes in body tissues. This allows the virucidal activity to occur within the body in the absence of external light sources. Another plant-derived compound, betulinic acid, which prevents entry of HIV into the target cell and may act also at the maturation stage, is being developed in a nanosomal formulation by Aphios. A combination therapy (bryostatin-1 plus histone deacetylase inhibitors) is also in development.

In March 2004, Aphios Corporation executed a material transfer agreement with the National Cancer Institute (NCI), National Institutes of Health (NIH) to access its natural products repository of terrestrial plants and marine organisms to discover and develop novel anticancer and antiviral therapeutics.

In March 2009, Aphios entered into a Collaborative Research and Development Agreement with VivaCell Biotechnology España SL to develop a combination therapy (bryostatin-1 plus histone deacetylase inhibitors), for the treatment of HIV latency.

Patent Information

Aphios Corporation was awarded a US patent (No. 7 037 534 B2) for chemiluminescence-activated antiviral therapeutics.

6. Marketed HIV Drug Clincal Profile by Company & Country

This chapter gives comprehensive insight on marketed 37 HIV drugs.

HIV Drig Profile: Abacavir

Alternate names	1592; 1592U89; Abacavir sulfate; VIROL®; Ziagen; Ziagen®; Ziagenavir
Originator	GlaxoSmithKline
Highest development phase	Marketed (Argentina, Australia, Brazil, Canada, European Union, France, Germany, India, Israel, Japan, Mexico, New Zealand, Puerto Rico, Spain, Thailand, United Kingdom, Uruguay, USA)
Active Development - indications	HIV infections
Class	Cyclopentanes, Dideoxynucleosides, Small-molecules
Mechanism of action	Nucleoside reverse transcriptase inhibitors
- WHO ATC code	J05A-F06 (Abacavir)
- EphMRA ATC code	J5C (HIV antivirals)

Owner/Originator/Collaborator/Licensee

Name	Role	Country	Type	Ownership
ChiroTech Technology Ltd	Collaborator	USA	Technology provider	Public
GlaxoSmithKline	Originator	England	Large Pharma, Pharmaceutical	Public
GlaxoSmithKline	Owner	England	Large Pharma, Pharmaceutical	Public
University of Minnesota	Technology Provider	USA	University	N/A

Brand Name

Organisation	Country	Indication	Brand Name
Ranbaxy Laboratories	India	HIV infections	VIROL®
GlaxoSmithKline	World	HIV infections	Ziagen®

Development Phase

Phase	Indication	Country	Route
Marketed	HIV infections	Argentina	PO
Marketed	HIV infections	Australia	PO
Marketed	HIV infections	Brazil	PO
Marketed	HIV infections	Canada	PO
Marketed	HIV infections	European Union	PO
Marketed	HIV infections	European Union	PO
Marketed	HIV infections	France	PO
Marketed	HIV infections	Germany	PO
Marketed	HIV infections	India	PO
Marketed	HIV infections	Israel	PO
Marketed	HIV infections	Japan	PO
Marketed	HIV infections	Mexico	PO
Marketed	HIV infections	New Zealand	PO
Marketed	HIV infections	Puerto Rico	PO
Marketed	HIV infections	Spain	PO
Marketed	HIV infections	Thailand	PO
Marketed	HIV infections	United Kingdom	PO
Marketed	HIV infections	United Kingdom	PO
Marketed	HIV infections	Uruguay	PO
Marketed	HIV infections	USA	PO
Marketed	HIV infections	USA	PO

Introduction

Abacavir is a carbocyclic 2'-deoxyguanosine nucleoside analogue. It is formulated as the sulfate and metabolised intracellularly to the active metabolite carbovir triphosphate which competitively inhibits HIV reverse transcriptase and terminates proviral DNA chain extension. Glaxo Wellcome (now GlaxoSmithKline) originated and selected abacavir for further development after evaluation of a wide variety of carbocyclic nucleoside analogues with modifications designed to optimise the bioavailability, toxicity and CNS penetration characteristics of carbovir. It is launched for the treatment of HIV-infections in over 45 countries worldwide. GlaxoSmithKline (GSK) is the marketing authorisation holder for abacavir-containing medicines. Previously, Glaxo Wellcome licensed the rights to related technology, including intermediates used in the manufacture of abacavir, from the University of Minnesota in 1992.

Patent Information

GSK settled a patent lawsuit filed against it by the University of Minnesota, relating to patents held by the university for compounds used in the manufacturing process of abacavir. The settlement required GSK to pay royalties to the university on worldwide sales of the drug. The patent on abacavir is due to expire in 2012 in the US and 2014 in the EU.

HIV Drug Profile: Atazanavir

Alternate names	Atazanavir sulfate; Atazor®; BMS-232632-05; CGP 73547; Reyataz®; TAZ
Originator	Novartis
Highest development phase	Marketed (Argentina, Australia, Brazil, Canada, Chile, European Union, Hong Kong, India, Indonesia, Israel, Japan, Malaysia, Mexico, New Zealand, Peru, Russia, Singapore, South Africa, Thailand, USA)
Active Development - indications	HIV-1 infections
Class	Oligopeptides, Pyridines, Small-molecules
Mechanism of action	HIV protease inhibitors
- WHO ATC code	J05A-E08 (Atazanavir)
- EphMRA ATC code	J5C2 (Protease inhibitors)

Owner/Originator/Collaborator/Licensee

Name	Role	Country	Type	Ownership
Bristol-Myers Squibb	Development Licensee	World	Large Pharma, Biopharmaceutical	Public
Bristol-Myers Squibb	Market Licensee	World	Large Pharma, Biopharmaceutical	Public
Emcure Pharmaceuticals	Sub-licensee	India	Pharmaceutical	
Gilead Sciences	Technology Provider	USA	Large Pharma, Biopharmaceutical	Public
Novartis	Originator	Switzerland	Large Pharma, Pharmaceutical	Public
Novartis	Owner	Switzerland	Large Pharma, Pharmaceutical	Public

Brand Name

Organisation	Country	Indication	Brand Name
Emcure Pharmaceuticals	India	HIV-1 infections	Atazor®
Bristol-Myers Squibb	World	HIV-1 infections	Reyataz®

Development Phase

Phase	Indication	Country	Route
Marketed	HIV-1 infections	Argentina	PO
Marketed	HIV-1 infections	Australia	PO
Marketed	HIV-1 infections	Brazil	PO
Marketed	HIV-1 infections	Chile	PO
Marketed	HIV-1 infections	Hong Kong	PO
Marketed	HIV-1 infections	India	PO
Marketed	HIV-1 infections	Indonesia	PO
Marketed	HIV-1 infections	Israel	PO
Marketed	HIV-1 infections	Japan	PO
Marketed	HIV-1 infections	Malaysia	PO
Marketed	HIV-1 infections	Mexico	PO
Marketed	HIV-1 infections	New Zealand	PO
Marketed	HIV-1 infections	Peru	PO
Marketed	HIV-1 infections	Russia	PO
Marketed	HIV-1 infections	Singapore	PO
Marketed	HIV-1 infections	South Africa	PO
Marketed	HIV-1 infections	Thailand	PO
Marketed	HIV-1 infections (Combination therapy, In adolescents, In children)*	European Union	PO
Marketed	HIV-1 infections (Treatment-experienced)	Canada	PO
Marketed	HIV-1 infections (Treatment-experienced)	European Union	PO
Marketed	HIV-1 infections (Treatment-experienced)	USA	PO
Marketed	HIV-1 infections (Treatment-naive)	Canada	PO
Marketed	HIV-1 infections (Treatment-naive)	European Union	PO
Marketed	HIV-1 infections (Treatment-naive)	USA	PO
III	HIV-1 infections (Combination therapy, In children, In infants)**	South Africa	PO
III	HIV-1 infections (Combination therapy, In children, In infants)**	South America	PO
III	HIV-1 infections (Combination therapy, In children, In infants)**	Thailand	PO
III	HIV-1 infections (In children, In infants)***	USA	PO

* In paediatric patients aged six to eighteen years and greater than 15kg.

** In paediatric patients aged three months to six years of age; in combination with ritonavir + Nucleoside Reverse Transcriptase Inhibitor

*** In paediatric patients aged three months to six years of age

Introduction

Atazanavir (Reyataz®) is a potent azapeptide inhibitor of HIV protease developed by Bristol-Myers Squibb (BMS) for use in the treatment of HIV-1 infections in combination with other antiretroviral therapies (ART). The compound selectively inhibits the virus-specific processing of viral Gag and Gag-Pol polyproteins in HIV-1 infected cells, preventing the formation of mature virions. Novartis Pharma discovered the compound and licensed worldwide development and marketing rights to BMS in June 1997. Atazanavir was the first once-daily protease inhibitor approved by the US FDA and the EMEA as part of combination therapy for the treatment of HIV/AIDS in adults. While overall, the side effects of atazanavir are comparable to that of other currently available protease inhibitors, atazanavir is unique in that does not increase cholesterol and triglyceride level in patients. Atazanavir was launched in the US in July 2003 and in the EU during 2004.

The product is available in an oral capsule formulation in strengths containing the equivalent of 100mg, 150mg, 200mg or 300mg of atazanavir as atazanavir sulfate. It is now widely available for use in combination with low-dose ritonavir and other antiretroviral therapies, in both treatment-experienced and treatment-naive patients with HIV-1 infections, in adults and children (over 6 years of age). Phase III development is ongoing in children less than 6 years old.

Bristol-Myers Squibb and Gilead are now collaborating on the development of a fixed-dose combination of atazanavir and the pharmaco-enhancing agent cobicistat. Matrix Laboratories (later Mylan Laboratories Limited), a subsidiary of Mylan Inc, obtained tentative approval from the US FDA for its ANDA for atazanavir (150 and 300mg) capsules and the product will be available outside the US in certain developing countries.

The approval was received in October 2010 under the President's Emergency Plan for AIDS Relief (PEPFAR). Matrix signed an immunity-from-suit agreement with BMS in June 2011 to expand access to atazanavir. The agreement allows the generic company to manufacture and sell atazanavir, as well as stavudine and didanosine, in sub-Saharan Africa and India.

Bristol-Myers Squibb announced a technology transfer agreement with the Brazilian Ministry of Health in November 2011 to expand access to atazanavir in Brazil. The

agreement transfers manufacturing and distribution in Brazil of atazanavir sulfate 200mg and 300mg capsules from Bristol-Myers Squibb to Farmanguinhos (a unit of the Oswaldo Cruz Foundation) and an unnamed local manufacturer of active pharmaceutical ingredients.

In February 2006, Bristol-Myers Squibb entered an outsourcing licensing agreement with Emcure Pharmaceuticals to manufacture and supply atazanavir in India. Emcure will also have a royalty-free licence to make and sell atazanavir in India as a generic. Atazanavir, known as Atazor®, was launched in India in late 2009 for the treatment of HIV-1 infections.

Patent Information

Market exclusivity for atazanavir is expected to expire in 2017 in the US, Canada and China and 2019 in major EU countries and Japan. Data exclusivity in the EU expires in 2014.

About KuicK Research

Kuick Research is a market research and analytics company that provides targeted information for critical decisions at business, product and service levels. We are quick, predictive and known by the recommendations we have made in the past. Our result-oriented research methodology offers understanding of multiple issues in a short period of time and gives us the capability to keep you full with loads of practical ideas. By translating research answers into strategic insight and direction, we not only rate the success potential of your products and/or services, but also help you identify the opportunities for growth in new demographies and find ways to beat competition.

Our audience measurement techniques, global research plan and execution, and modern resolutions to taxing research issues make a difference to our clients' performance at the ground level. We follow a thorough approach to provide you accurate insights and ensure that everything fits well with your business objectives. We can do single or multi-country studies, track your programmes, do an interviewer-led research, run syndicated programmes or give you the data back with detailed recommendations. We also support our market research project with suggested 'next steps' and advice on tying these steps with your company's overall strategy.

As a global research company, we are creative enough to think differently and use our experience to address your questions, as well as the benefits and/or drawbacks of various research solutions. We use several services including syndicated research solutions, custom research reports, data-collection services, competitor-tracking intelligence, consumer behaviour studies and consulting to give you a holistic answer, that will save you time, energy and efforts in the long run. We serve multiple industry verticals in private and government segments. Multinationals, medium and small enterprises contact us to find better solutions to help them meet the needs of their consumers, and predicting where they should head next.

Kuick Research also runs two separate portals - Orphan-drug.com, that provides high-end intelligence, research and consulting services in Orphan Drug market, and Researchreportindia.com that caters to the needs of clients seeking growth in the Indian market by carrying out trustworthy intelligence on factors like market overview, market dynamics, government rules, regulation and policy framework.