Antiviral Research 79 (2008) 143–165

Contents lists available at ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

Review

A survey of the syntheses of active pharmaceutical ingredients for antiretroviral drug combinations critical to access in emerging nations

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ARTICLE INFO

Article history:
Received 29 October 2006
Accepted 5 May 2008

Keywords:
HIV-1
Drugs
Second line
Synthesis
Prices
Efavirenz
Tenofovir Disoproxil Fumarate
TDF
Emtricitabine
FTC
Ritonavir
Lopinavir
Kaletra
Atazanavir

ABSTRACT

It has been roughly 25 years since the threat posed by human immunodeficiency virus type 1 (HIV-1) became widely known. The cumulative death toll from HIV/AIDS is now greater than 25 million. There are approximately 33 million people living worldwide with this disease, of whom about 68% (22.5 million) live in sub-Saharan Africa (http://www.avert.org/worldstats.htm). A number of antiretroviral (ARV) drugs have been approved for treatment of HIV/AIDS. Inhibitors of HIV reverse transcriptase (RTIs) include the nucleoside/nucleotide drugs zidovudine, lamivudine, abacavir, didanosine, stavudine, emtricitabine and tenofovir disoproxil fumarate. Non-nucleoside RTIs include nevirapine, efavirenz and etravirine. Inhibitors of HIV protease (PIs) include saquinavir, ritonavir, lopinavir, nelfinavir, indinavir, fosamprenavir and atazanavir. Enfuvirtide inhibits the HIV fusion protein. The CCR5 chemokine antagonist maraviroc and the integrase inhibitor raltegravir were very recently approved by the US FDA. Fixed-dose combinations (FDCs) have been formulated to increase tolerability, convenience and compliance. First-line drug combinations are offered to treatment-naive patients, while second-line drugs are reserved for those who no longer respond adequately to first-line therapy. In developing countries a modest but increasing fraction of those infected have access to ARVs. The Clinton HIV/AIDS Initiative estimates that 2.4 million of the nearly 8 million individuals needing treatment in developing nations have access to some drugs. First-line FDCs used in resource-poor settings are largely combinations of two nucleoside RTIs and a non-nucleoside RTI or PI. The effectiveness of these combinations decreases over time, requiring a switch to combinations that retain potency in the presence of viral resistance. Increasing access to second-line FDCs and new developments in first-line ARV therapy are cost challenges. In high-income countries the cost of ARV therapy is largely irrelevant, except for "advanced salvage" drugs such as enfuvirtide. In resource-poor settings cost is a huge factor that limits drug access, resulting in high rates of new infection and subsequent mortality. IP coverage, where granted, can keep access prices for essential ARVs higher than would otherwise be the case. Large, innovator companies have made drugs available at prices very close to the cost of manufacturing for "lowest income" countries. Generic providers in India and elsewhere provide the largest supply of drugs for the developing world. The recent issuance of Voluntary and Compulsory Licenses (VLs, CLs) through the World Trade Organization's TRIP (Treaty Respecting Intellectual Property) provisions arguably contribute to bringing down access prices. The utilization of improved science, pooled purchasing and intelligent procurement practices all definitely contribute to access. This work surveys the production processes for several critical ARVs. These are discussed in terms of scale up, raw material/intermediates and active pharmaceutical ingredient (API) costs. In some cases new routes to APIs or critical intermediates are needed. Based on potential new chemistries, there are significant opportunities to reduce cost for a number of critical ARVs.

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doi:10.1016/j.antiviral.2008.05.001

Contents

1. Introduction

Although the death toll from HIV/AIDS over the last quarter century has reached many millions, AIDS has become a manageable chronic disease. An impressive range of compounds (exactly 25) have so far been approved for HIV/AIDS treatment (De Clercq, 2007). Combination therapy with three or more antiretrovirals (ARV) provides relief of symptomatic disease, with most patients achieving increased CD4 levels and undetectable viral load in circulating blood plasma. Significant progress has been made for increased access to ARVs, with over 2 million patients in developing countries receiving ARVs at this time (1Q2008). The fixed-dose combination (FDC) "triomune™" (AZT + 3TC + nevirapine) from Cipla presently sells for approximately $95–140 per patient year, and is the standard first-line FDC in many developing countries. The demonstrated clinical superiority of "Atripla®" (EFV + TDF + FTC) (De Clercq, 2006) and new WHO recommendations have created significant pressure to establish this as a new standard for first-line treatment. One of the major constraints for treatment access is cost. Approximately 65–90% of the cost of ARV therapy derives from the active pharmaceutical ingredient (API).

There is an urgent need to find cheaper alternatives for the production of critical ARVs. This paper discusses methods of producing the APIs efavirenz, emtricitabine, tenofovir disoproxil fumarate, abacavir, ritonavir, lopinavir and atazanavir. With increasing need for improved therapies, there is a strong economic interest in the production of these compounds. This paper describes the most useful commercial processes to produce these compounds. The present work is not exhaustive, but aims to analyze the present situation concerning production costs and favorable alternatives.

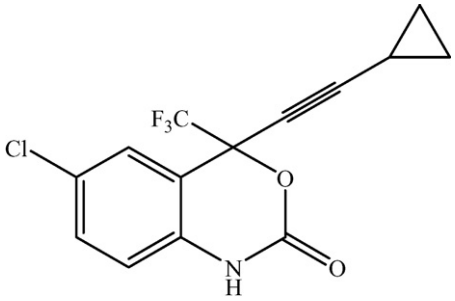
Previous reviews (for example, Izawa and Onishi, 2006; De Clercq, 2001, 2005; Painter et al., 2004; Rodriguez-Barrios and Gago, 2004; Stolk and Lüers, 2004; Peçanha et al., 2002; De Clercq, 1998; Flexner, 1998; Wlodawer and Vondrasek, 1998; Antunes, 1996) emphasized the synthesis of particular classes of compounds or disclosed the development of these APIs.

2. Background

API costs represent a substantial majority of the overall cost of a finished dosage form. The synthesis of an API usually requires several chemical processing steps in which new chemical bonds are formed and molecular complexity increases. API processes are normally carried out in solution, thereby limiting overall process efficiency. Formulation of APIs into a finished dosage form is usually a single process without a change in molecular complexity. Formulation processes typically utilize modest amounts of water, ethanol or no solvent, and additional ingredients (excipients) that are less expensive than the API. Much of the cost of formulation is associated with API losses during processing. Innovation to reduce API costs is therefore a natural focus for reducing price. Cost information in this paper was obtained directly from manufacturers of fine chemicals and generic ARVs. Price quotations from specific companies can only be judged within a framework that includes timing, volume, exchange rates and cost of raw materials. For this reason we will not attribute costs for APIs or intermediates to a specific company, unless this information is already available or has been agreed to by the supplier. The prices for APIs represent the cost of manufacturing plus a profit. In general, ARV APIs are sold at roughly 20% above the cost of production on a scale of several metric tons or more. A rough rule-of-thumb has been made for estimating the large-scale cost of key reagents and new molecules from prices available in the Sigma–Aldrich catalogue for laboratory supply (Laird, 2005). Although this is particularly useful for general purposes, we have not used this yardstick. All prices provided in this paper represent quotes provided by commercial vendors at "representative" production volumes that range from 1 metric ton upwards.

3. Efavirenz

Efavirenz (EFV) was discovered at the Merck Research Laboratories and licensed to Dupont Pharmaceuticals. Dupont carried EFV through development and commercialization. It is marketed as Sustiva® (Bristol-Myers Squibb) and Stocrin® (Merck). Young et al. (1996) obtained the original patent on the synthesis and HIV RT inhibition properties of efavirenz (**5**). Other researchers have improved this process (Radesca et al., 1997; Patel et al., 1999a,b, 2000). The initial synthesis of **5** as a racemate was followed by resolution through the *N*-camphanic imide to yield efavirenz with good (>98% e.e.) enantiomeric purity.



rac-Efavirenz

The conversion of **2**–**2b** by use of a directed *ortho*-metalation reaction (DOM; Snieckus, 1990) is a convenient means of introducing a trifluoromethyl ketone *ortho* to the amine function of **3**, isolated as the hydrochloride hydrate.