

# NEW ORAL ANTICOAGULANTS MARKETS

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**Trends, Industry Participants, Product Overviews and Market Drivers**

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## 1. Introduction

Anticoagulants are sometimes referred to as blood thinners, as they help in preventing blood clots from forming to minimize the risk of heart attack, stroke and blockages in arteries and veins. However, anticoagulants cannot break up the blocks that have already been formed in the arteries and veins. Anticoagulants are prescribed for patients with heart valve implants, atrial fibrillation (irregular heart beat) and cardiomyopathy that increase the risk of developing blood clots. Though they are called blood thinners, in reality, they do not thin the blood but simply decrease the ability of the blood to create harmful blood clots that may potentially block the arteries and vein, ultimately leading to a heart attack or stroke. For more than 50 years and until recently, the only oral anticoagulants were the vitamin K antagonists such as warfarin. Within the past few years, several new oral anticoagulants (NOACs) have entered the market. These products, such as Pradaxa (dabigatran) and Xarelto (rivaroxaban), are commercially available, and Eliquis (apixaban) is expected to be approved in the United States (U.S.) and European Union (E.U.). These and the other new oral anticoagulants in the horizon have several advantages over warfarin. They do not interact with food or other drugs, and thus produce a predictable effect with fixed doses. They need no periodical laboratory monitoring, and thus they are more convenient to administer than warfarin. This TriMark Publications report provides a thorough overview of the new oral anticoagulants, their approved indications, drug profiles, pharmacokinetic parameters and the respective areas of market growth with projections.

### 1.1 Scope of this Report

The report provides a thorough overview of anticoagulants, including FDA-approved indications, pharmacokinetic parameters, areas of market growth and unmet medical needs. The near-term and expected changes paved by the introduction of oral anticoagulants and the prophylactic market will be assessed in light of market opportunities and influence of at least two new therapeutic options expected to reach commercialization. The second chapter of this report provides an insight into the structure and mechanism of action of the key oral anticoagulants of interest, dabigatran, rivaroxaban, apixaban and edoxaban, as well as other pipeline agents within this class. Also cataloged are selected parenteral anticoagulants such as unfractionated heparins (UFH); low molecular weight heparins (LMWH); dalteparin (Fragmin); enoxaparin (Lovenox); fondaparinux (Arixtra); and tinzaparin (Innohep). Anticoagulants therapy is necessitated in most of the surgical procedures except the cosmetic surgeries; the third chapter of this report deals with the global and regional markets for surgical applications, such as for orthopedic procedures. The fourth chapter of this report is the largest section and it deals with the market analysis of the various anticoagulants and antiplatelet drugs available in the market. This section also offers an insight into the drugs that are slowly getting phased out of the market and the newer drugs that poised to reshape the market. The fifth chapter of this report gives brief accounts of the profiles of companies that are focused on developing and marketing anticoagulant drugs. The appendix section of this report provides valuable information on the market trends for various pharmaceutical drugs in the global and U.S. level.

### 1.2 Methodology

The authors of this report include a tenured Ph.D.-trained (University of California) professional with extensive experience with the cardiovascular treatment landscape, and, a retired professor of biochemical pharmacology with several years experience in market research. Company-specific information for this report has been obtained mainly from industry trade publications, academic journals, news and research articles, press releases and corporate websites, as well as annual reports for publicly-held firms. Additionally, sources of information include the non-governmental organizations (NGOs) and relevant medical societies.

Some of the statistical information was taken from Biotechnology Associates' databases and from TriMark's private data stores. The information in this study was obtained from sources in which TriMark has high confidence. TriMark cannot guarantee the accuracy, adequacy or completeness of any information or omission or for the results obtained by the use of such information. Key information from the business literature was used as a basis to conduct dialogue with and obtain expert opinion from market professionals regarding commercial potential and market sizes. Senior managers from major company players were interviewed for the purposes of this report.

### ***Primary Sources***

TriMark collects information from hundreds of Database Tables and many comprehensive multi-client research projects, as well as Sector Snapshots that we publish annually. TriMark extracts relevant data and analytics from TriMark's research as part of this data collection.

### ***Secondary Sources***

TriMark uses research publications, journals, magazines, newspapers, newsletters, industry reports, investment research reports, trade and industry association reports, government-affiliated trade releases and other published information as part of its secondary research materials. The information is then analyzed and translated by the Industry Research Group into a TriMark study. The Editorial Group reviews the complete package with product and market forecasts, critical industry trends, threats and opportunities, competitive strategies and market share determinations.

### ***TriMark Publications Report, Research and Data Acquisition Structure***

The general sequence of research and analysis activity prior to the publication of every report in TriMark Publications includes the following items:

- Completing an extensive secondary research effort on an important market sector, including gathering all relevant information from corporate reporting, publicly-available data and proprietary databases.
- Formulating a study outline with the assigned writer, including important items, as follows:
  - Market and product segment grouping, and evaluating their relative significance.
  - Key competitors' evaluations, including their relative positions in the business and other relevant facts to prioritize diligence levels and assist in designing a primary research strategy.
  - End-user research to evaluate analytical significance in market estimation.
  - Supply chain research and analysis to identify any factors affecting the market.
  - New technology platforms and cutting-edge applications.
- Identifying the key technology and market trends that drive or affect these markets.
- Assessing the regional significance for each product and market segment for proper emphasis of further regional/national primary and secondary research.
- Completing a confirmatory primary research assessment of the report's findings with the assistance of expert panel partners from the industry being analyzed.

### **1.3 Executive Summary**

The anticoagulants market is on the threshold of a potential major shift in clinical practice, from a market monopolized by a single, injectable anticoagulant to a highly competitive market dominated by newer oral anticoagulants. There is intense activity in the anticoagulant drug development space as companies are competing with each other to launch novel therapies which offer superior safety, efficacy and convenience to patients and physicians, a medical need which has gone unfulfilled for decades. In [REDACTED], the global market for warfarin stood at about \$ [REDACTED]. Warfarin has been in the anticoagulants market for more than 50 years and with the introduction of new drugs in the recent past, improved options will capture a large share of the market. The cost savings of warfarin, however, as well as continuity for patients doing well with warfarin, will keep warfarin a significant part of the market indefinitely. Yet, due to convenience of use and other factors of other agents, warfarin is expected to lose its ground and give way to other oral anticoagulants in the near future. Present market trends indicate that warfarin may gradually become phased out in [REDACTED] or [REDACTED]. Yet, it is a remarkable survival rate for a drug that dominated the anticoagulation sector for more than 50 years.

Two agents, classified as ‘newer oral anticoagulant drugs’ have begun entering the market and are expected to recast antithrombotic therapy by offering effective, less cumbersome alternatives to the standard of care for chronic anticoagulation warfarin. These drugs are Pradaxa (dabigatran), an oral direct thrombin inhibitor; Xarelto (rivaroxaban), an oral factor Xa inhibitor; Eliquis (apixaban), an oral factor Xa inhibitor; and edoxaban, also an oral factor Xa inhibitor. In the U.S. more than [REDACTED] prescriptions have been filled for Pradaxa 150 mg and more than [REDACTED] atrial fibrillation patients have been prescribed with Pradaxa 75 mg since its approval in [REDACTED]. The global market for dabigatran was worth about \$ [REDACTED] in [REDACTED] and this market will have a value of about \$ [REDACTED] in [REDACTED]. In Canada, where the national healthcare system views the convenience of oral anticoagulants therapy as superior to warfarin, uptake has been even more rapid.

The once-daily dosing of Xarelto is a plus. Both Pradaxa and Xarelto are cleared renally. Xarelto also has limited hepatic clearance. For patients with renal impairment, warfarin may remain the best option. Otherwise use of concomitant medications may factor into treatment choice. The half-life of Xarelto is the shorter of the two; for patients (or physicians) concerned about drug reversal, this may or may not be a differentiator.

For the prophylaxis of venous thromboembolism, rivaroxaban represents a broader therapeutic window, less monitoring, and easier dosing than heparin or Arixtra. It also has a decreased risk for thrombocytopenia as compared to Arixtra. Eli Lilly’s LY-517717 is slated to enter the market in [REDACTED] and appears to possess comparable efficacy and possibly superior safety than existing agents.

Rivaroxaban has been in the U.S. market since [REDACTED]. Globally, rivaroxaban had a market valued at \$ [REDACTED] in [REDACTED] and this figure is predicted to reach \$ [REDACTED] in [REDACTED]. Though some analysts consider apixaban (Eliquis) the future front-runner based on its slightly superior profile, it will need to overcome third-to-market status. Eliquis (apixaban; BMS/PFE) received EMA approval most recently, on [REDACTED]; with FDA approval anticipated by [REDACTED]. Accordingly, the success of its market launch is yet to be gauged. Edoxaban is from Daiichi Sankyo and the company received marketing approval in [REDACTED] from the Japanese Ministry of Health, Labor and Welfare. This oral anticoagulant is yet to make its impact in the global market. Edoxaban is a once-daily oral anticoagulant that is currently available only in Japan.

These newer oral anticoagulants are poised to become the standard of care for stroke prevention for atrial fibrillation patients. The directionality and magnitude of the mortality reduction is consistent and approximates a reduced relative risk of [REDACTED]% per year. These drugs are also expected to seize significant market share from the injectable anticoagulants for prophylaxis of venous thromboembolism in orthopedic surgery. The major shaper yet to be seen is in physician education. Whereas warfarin is managed by specialists adept with the nuances of the agent—at Coumadin clinics—the availability of oral anticoagulants puts anticoagulation into the hands of nonspecialists. It should be noted that although oral anticoagulants are less “finicky” than warfarin, blood thinning inherently requires monitoring and intimate familiarity with the drug interactions and other drug attributes. Oral anticoagulants are far less safe than traditional agents used for cardiovascular disorders, such as ace inhibitors or statins. In the case of these preventative agents, preventative cardiologists, internists, and even community family doctors can be at ease in managing the potential safety, adherence and drug interactions of the agents. In the present case, however, a prescriber physician needs to be fully versed and conducting monitoring to ensure that the extent of anticoagulation is appropriate. Too little, and the patient remains at risk. Too much, and the patient can sustain internal bleeds that can prove fatal. Moreover, both patient and physician must be fully educated on the half-life of the particular, to be taken into account before any surgical or invasive procedure.

Despite the staggering opportunity afforded through long-term, prophylactic acute coronary syndrome (ACS) market, imperfections in this patina are starting to appear. Bleeds are inherent of any anticoagulant therapy. In [REDACTED], the FDA released the findings of the SENTINEL Study, a postmarketing insurance claims database analysis of dabigatran bleeds and found, rather conclusively, that bleed rate does not exceed that of warfarin.

An important consequence of the nuances of the individual newer oral anticoagulants is that a given physician and institution is likely to choose one oral anticoagulant for use in most patients. This would be a practical, even advisable, step towards increasing safety, efficacy and tolerability with the use of newer oral anticoagulants. Indeed, TriMark experts who have been among the hundreds of investigators remain adopters of Pradaxa or Xarelto and on which they have clinical experience.

Both “camps” are happy with their choice of therapy, but few of TriMark’s opinion leaders report switching between the two available agents, although both are on formulary. Only the savviest prescribers report that they have built comfort and use both extensively in their clinical practice; drug of choice being driven by patient profile. Most, however, maintain a “go to” drug for the vast majority of their scripts, and resort to the other option only when necessary based on patient profile.

Expert opinion is consistent that the commercialized and emerging oral anticoagulants are overall comparable in efficacy. Although each agent may be shown to excel for one patient population or indication—or in a particular clinical trial (given its particular study design and cohort), members of this class are largely viewed as equally acceptable drug options. Treatment of choice will likely be determined by the patient-specific variables, including drug-Drug interactions and preferred route of clearance. Towards this end, it may be expected that patients will be often referred to the care of a cardiologist or anticoagulations clinic.

Injectable anticoagulants have hospital-based critical care applications, mainly for cardiac indications, for which rapid acting, reversible agents are well suited. Drugs such as Lovenox (enoxaparin sodium), Arixtra (fondaparinux sodium), Fragmin (dalteparin sodium) and Angiomax (desirudin) along with unfractionated heparin (UFH) will likely stay put and dominate critical care due to their advantageous pharmacological properties. Unfractionated heparins have been in clinical use for several years but their position is being threatened with the arrival of other new anticoagulants. In its heydays, it enjoyed a market share of more than \$ [REDACTED], but in [REDACTED] its market was valued only at \$ [REDACTED] and this is further expected to decline and reach only \$ [REDACTED] in [REDACTED]. Same is the case with low molecular weight heparins. The LMWH had a market of about \$ [REDACTED] in [REDACTED], but it is expected to decline steeply and reach \$ [REDACTED] in [REDACTED]. Sanofi-Aventis’ Lovenox is also seriously threatened by a generic copycat version. The anticoagulants market is forecast to experience significant growth during the analysis period as premium priced therapies gradually replace the widely used inexpensive generic warfarin, while at the same time attracting new patients previously left untreated with no therapeutic options. Safety, mainly with regard to bleeding, is a key for regulatory, patient and physician acceptance of new therapies, and it is understood that this factor will primarily drive market share for emerging anticoagulant drugs.

In the recent past, several new antiplatelet drugs have been approved to expand the armory of the treating physician. Until a few years ago, clopidogrel (Plavix) dominated the oral antiplatelet market with a [REDACTED]% share. Clopidogrel lost patent protection in Europe in [REDACTED], and in the U.S. it is to lose the patent rights in [REDACTED]. This has caused sales of this drug to plummet to less than [REDACTED]% of former sales highs. Plavix had a market worth of about \$ [REDACTED] in [REDACTED], and it is predicted that the drug will survive only up to [REDACTED] when its market value will be only about \$ [REDACTED].

Prasugrel (Effient) is an oral antiplatelet drug that targets platelet aggregations. It was discovered by Daiichi Sankyo and its Japanese research partner Ube Industries Ltd. It is now being marketed by Daiichi Sankyo and Eli Lilly and Company. The global market for prasugrel in [REDACTED] was worth about \$ [REDACTED] and the favorable market for the drug indicates that it will grow and reach \$ [REDACTED] in [REDACTED]. Pharmaceutical industry analysts have tipped prasugrel as a potential blockbuster. The other antiplatelet drugs available in the market are pletal, activase, aggrenox, cardioaspirin, opalman, integrillin and ReoPro. Except integrillin and ReoPro, all the other antiplatelet drugs have been witnessing a growing market.