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GlobalData
PharmaPoint

ATRIAL FIBRILLATION – GLOBAL DRUG FORECAST AND MARKET ANALYSIS TO 2023

Executive Summary

Table below provides the key metrics for atrial fibrillation (AF) in the eight major pharmaceutical markets (8MM) (US, France, Germany, Italy, Spain, UK, Japan, and Canada) covered in this report, from 2013 to 2023.

AF: Key Metrics in the 8MM, 2013–2023	
2013 Epidemiology	
Prevalent population	10.1 million
Treated population	8.7 million
2013 Market Sales	
US	$2.7bn
5EU	$1.4bn
Japan	$258m
Canada	$243m
Total	**$4.6bn**
Pipeline Assessment	
Number of drugs in Phase I–III	10
Number of first-in-class drugs	1
Most Promising Pipeline Drug	**Peak-Year Sales**
Gilead's ranolazine/dronedarone	$315m
Key Events (2014–2023)	**Level of Impact**
Launch of Daiichi Sankyo's Savaysa* (edoxaban) in 2014 and 2015	↑↑
Portola Pharmaceuticals launches the factor Xa inhibitor antidote, andexanet alfa, in 2017	↑↑
Boehringer Ingelheim launches the Pradaxa antidote, idarucizumab, in 2018	↑↑
Boehringer Ingelheim's Pradaxa (dabigatran) loses US patent protection in 2018	↓↓↓
Gilead launches ranolazine/dronedarone in 2022	↑↑
2023 Market Sales	
US	$2.4bn
5EU	$2.5bn
Japan	$535m
Canada	$255m
Total	**$5.7bn**

Source: GlobalData
*Edoxaban is marketed as in Japan under the brand name Lixiana.
5EU = France, Germany, Italy, Spain, and the UK, 8MM = US, France, Germany, Italy, Spain, UK, Japan, and Canada

Atrial Fibrillation Market Will Peak at $9.4bn in 2020

GlobalData estimates the 2013 sales for AF at approximately $4.6 billion across the 8MM. The US dominates the overall size of the AF market, generating an estimated $2.7 billion in 2013 and accounting for 59% of the overall size of the market. This is mainly due to the large prevalent AF population in the US, early adoption of the new oral anticoagulants (NOACs), and higher prices for AF medications in this market.

Since the launch of the first of the NOACs in 2010, this drug class has experienced substantial uptake, accounting for $3.2 billion − approximately 70% − of all AF sales revenue across the 8MM in 2013. GlobalData anticipates that NOAC uptake will continue to increase, and will be the main driver in the growth of the AF market. This growth will be driven further by the recent launch of a fourth NOAC, Daiichi-Sankyo's Savaysa, which now provides further anticoagulant treatment options for patients with AF. GlobalData forecasts that the AF drug market will grow at a Compound Annual Growth Rate (CAGR) of 2.1% over the 10-year forecast, resulting in a market value of $5.7 billion by 2023. However, it is expected that peak sales will be reached prior to this date, in 2020, when the AF market will be valued at $9.4 billion. A subsequent decline in the overall size of the AF market from this date will be related to the entry of the first generic versions of the NOACs, starting

Executive Summary

with Boehringer Ingelheim's anticipated loss of US patent protection for Pradaxa in 2018.

The antiarrhythmic drugs ranolazine/dronedarone, developed by Gilead, and Laguna Pharmaceuticals' vanoxerine are also forecast to launch late in the forecast period. However, neither will reach peak sales by 2023, with only ranolazine/dronedarone making an early impact as a potential drug candidate for the maintenance of sinus rhythm.

Major drivers for the growth of the AF market over the forecast period will include:

- The continued uptake of the NOACs for the prevention of stroke in patients with AF. Due to the advances that the NOACs provide in terms of improved safety and the lack of a need for routine monitoring, NOAC uptake will continue to increase, taking market share away from warfarin.
- A shift in AF treatment guidelines to using the CHA_2DS_2-VASc score instead of the $CHADS_2$ score for assessing stroke risk, which will cause a larger proportion of lower risk patients to receive anticoagulant treatment. (See Table 13 and Table 14 for descriptions of the $CHADS_2$ and CHA_2DS_2-VASc abbreviations, respectively.)
- The approval and launch of the first antidotes for the NOACs will alleviate physician and patient concerns regarding a lack of a reversal agent in the event of uncontrolled bleeding, thereby increasing overall uptake.

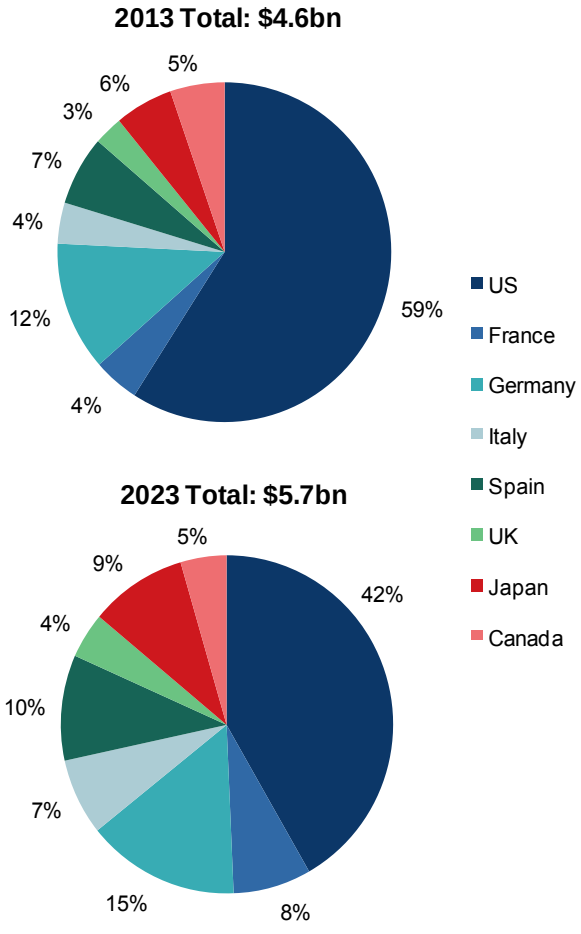
Major barriers to the growth of the AF market over the forecast period will include:

- Generic erosion of the NOACs, starting with Boehringer Ingelheim's Pradaxa, which will lose US patent protection in 2018.
- Large, costly, and comprehensive clinical trials required to support regulatory approval of cardiovascular drugs, which will deter drug developers wanting to enter the AF market.
- Widely available generic antiarrhythmic drugs, which will make it difficult for any novel rhythm control agents to gain reimbursement and wider uptake.

Executive Summary

Figure below provides the sales for AF in the 8MM from 2013 to 2023.

Sales for AF by Region, 2013–2023



Source: GlobalData

The New Oral Anticoagulants Will Drive the Growth and Size of the Atrial Fibrillation Market

Antithrombotic therapy has an important role in the prevention of stroke in patients with AF, with vitamin K antagonists such as warfarin historically being the most widely prescribed drugs and with antiplatelet drugs playing a more minor role. However, since 2010, and the launch of the first of the NOACs, a shift in the treatment of patients with AF has occurred. There are now four NOACs on the market indicated for the prevention of AF, which include Boehringer Ingelheim's Pradaxa (dabigatran), Bayer/Janssen's Xarelto (rivaroxaban), Bristol-Myers Squibb/Pfizer's Eliquis (apixaban), and a fourth NOAC which was only approved in the US early in 2015, Daiichi-Sankyo's Savaysa (edoxaban).

The NOACs represent important advances over warfarin because they have predictable pharmacological profiles and do not require routine blood monitoring or dose adjustments, have fewer drug–drug interactions, an absence of major dietary effects, and in terms of efficacy and safety, have proven to be non-inferior, if not superior, compared with warfarin, particularly with regard to a reduced risk of major bleeding. However, uptake of the NOACs has been slowed due to the associated cost of these drugs, which are substantially higher than that of generically available warfarin and other vitamin K antagonists. In addition, the lack of an antidote that can be used in the case of excessive bleeding with NOACs has also limited their widespread use. GlobalData believes that as physician familiarity with these drugs increases, and experience is gained in selecting the appropriate NOAC based on a patient's risk profile, further NOAC uptake will occur across all markets. The anticipated arrival of

Executive Summary

NOAC reversal agents (antidotes) from 2017 on are also expected to ease remaining physician and patient concerns regarding the treatment of uncontrolled bleeding.

GlobalData anticipates that the NOACs will have the greatest impact on the AF market within the forecast period. It is anticipated that the strong safety and efficacy profile of Eliquis, as demonstrated in pivotal Phase III clinical trials, will drive uptake of the drug, despite it being positioned as the third NOAC to enter the market. It is forecast that sales of Eliquis will exceed Xarelto by 2018 replacing it as the market leader of the NOACs. In contrast, the impact of the launch of Savaysa in the US is expected to be more limited than initially anticipated, after the US Food and Drug Administration (FDA) decided that Savaysa will carry a boxed warning stating that the drug should not be used in patients with normal renal function. With the anticoagulant space for the prevention of stroke becoming increasingly crowded, it is forecast that Pradaxa will be the NOAC to lose the most market share as physicians and patients opt for one of the other NOACs such as Xarelto and Eliquis, which not only have strong safety profiles, but also less restrictions on their use.

Companies Focus on Label Expansion and Intensive Marketing to Differentiate Their Products

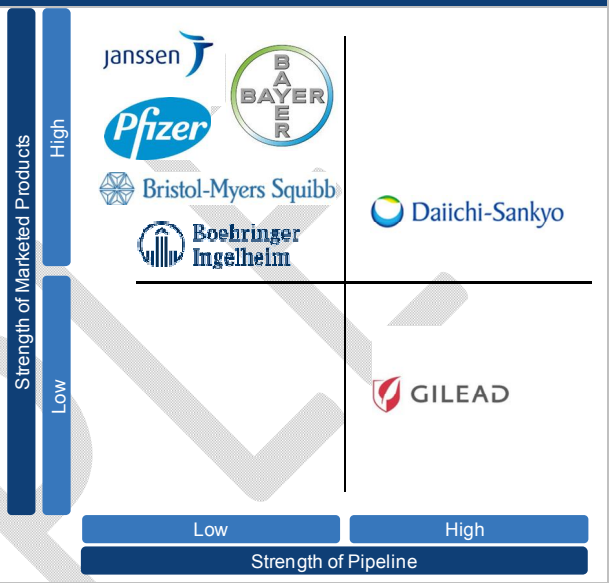
Companies attempting to penetrate the AF market and differentiate their products, particularly those companies that market NOACs, are doing so with two main strategies: label expansion to increase physician brand familiarity, and intensive marketing to disseminate clinical trial results. Gaining approval for additional cardiovascular indications has been a strategy that has worked very well for Bayer and Janssen, the two companies that jointly developed and market Xarelto. Positioned as the second-to-market NOAC, after Pradaxa, Xarelto's marketing companies rapidly conducted clinical trials and filed for regulatory approval for non-AF indications, such as the treatment and reduction in risk of recurrent deep vein thrombosis (DVT), pulmonary embolism (PE), and acute coronary syndrome (ACS), thereby initially garnering the approval for more indications than any of the other NOACs. Boehringer Ingelheim, Bristol-Myers Squibb, and Pfizer have tried to follow suit, but have been much slower at expanding the labels of their own respective NOACs. The competing companies have had difficulty in keeping up with the marketers of Xarelto, and Bayer and Janssen are now also pursuing Xarelto's approval for additional patient populations such as chronic heart failure, and the prevention of symptomatic venous thromboembolism (VTE) and VTE-related death in high-risk, medically ill patients.

Executive Summary

In addition to label expansion, marketing has also played a strong role in the success of certain NOACs. Bayer and Janssen, for example, heavily invested in advertising by utilizing journal articles and direct-to-consumer advertising as a means to reach physicians and patients, while Bristol-Myers Squibb and Pfizer have also reported that they have initiated marketing and outreach campaigns to disseminate the positive results from the pivotal Phase III clinical trials with Eliquis. Furthermore, some companies are using the results from additional clinical trials or subanalysis studies to differentiate their NOACs. Bayer and Janssen are the only companies to have conducted a clinical trial for a NOAC solely in a Japanese population (with the J-ROCKET AF study); the companies have strongly publicized this information, thereby giving Xarelto an advantage in Japanese clinical practice. Companies such as Bayer, Janssen, and Daiichi Sankyo are also conducting studies in subgroups of the AF population, such as patients scheduled for cardioversion or catheter ablation, as a way of differentiating their NOACs and cementing them as part of the standard of care in the anticoagulation of patients with AF.

Figure below provides a gap analysis of the major players in the AF market during the forecast period

Company Portfolio Gap Analysis in AF, 2013–2023



Source: GlobalData

Safer Antiarrhythmic Drugs Remains Biggest Unmet Need in Atrial Fibrillation Treatment

The overall level of unmet need in the AF market is moderate, with a number of generics available for the management of heart rate control, and the recent arrival and anticipated the launch of several NOACs for the prevention of stroke. However, even though there is now adequate therapeutics available for most AF management strategies, the biggest unmet need lies in safer antiarrhythmic drugs for the maintenance of sinus rhythm. Despite the restoration and maintenance of sinus rhythm being a common practice in the management of AF, the antiarrhythmic drugs that are available are

Executive Summary

of modest efficacy and have unfavorable safety profiles. For example, amiodarone is a widely used generic antiarrhythmic drug, and even though it is considered the most effective agent available for heart rhythm control, it has a number of side effects, including proarrhythmia as well as thyroid, liver, skin, and pulmonary complications. Subsequently, Sanofi's Multaq (dronedarone) was developed in the hope it would be an effective and safer alternative to amiodarone, but it was found to increase the risk of death in patients with permanent AF and some subtypes of heart failure.

Antiarrhythmic drug development has been very slow and there are very few drugs in the current pipeline that are expected to address this unmet need during the forecast period. At present, there are no antiarrhythmic drugs in Phase III clinical trials; however, there are six drugs in Phase II development and one drug in Phase I. Of these agents, the furthest in development is Gilead's fixed-dose combination (FDC) of ranolazine and low-dose dronedarone, which recently completed Phase II clinical trials for paroxysmal AF. Part of the reason for the low level of activity in the pipeline is due to the high risk involved in developing an antiarrhythmic drug. Large and costly clinical trials are required to demonstrate that a drug is safe and effective, and the track record for those antiarrhythmic drugs that have reached the market in the past decade has been disappointing. It is also expected that the availability of cheaper generic alternatives and the continuing cost constraints faced by national health authorities will also make it difficult for drugs to obtain reimbursement and subsequent addition to hospital formularies.

Outside of rhythm control strategies, the other key unmet needs that still exist are related to barriers to NOAC uptake, which include: antidotes that can successfully reverse the anticoagulant effect of the NOACs; improved access and reimbursement of the NOACs; and increased patient awareness and physician education on the clinical benefits of stroke prevention with these drugs.

New Oral Anticoagulant Market Becomes Increasingly Crowded as Antiarrhythmic Drug Pipeline Remains Sparse

The AF therapeutics pipeline can be divided into two categories of drugs: anticoagulants in development for the prevention of stroke in patients with AF, and antiarrhythmic drugs that can be used for the maintenance of normal sinus rhythm or to cardiovert patients with AF back to sinus rhythm. In the anticoagulant market, Daiichi-Sankyo's Savaysa (edoxaban) was approved for stroke prevention in Japan and the US, in September 2014 and January 2015, respectively, with regulatory approval in Europe still pending; making it the fourth NOAC to enter this space. However, Savaysa will encounter competition from established brands, such as Pradaxa, Xarelto, and Eliquis, which for some, have had several years to increase brand familiarity through indication expansion, marketing, and a larger collection of

Executive Summary

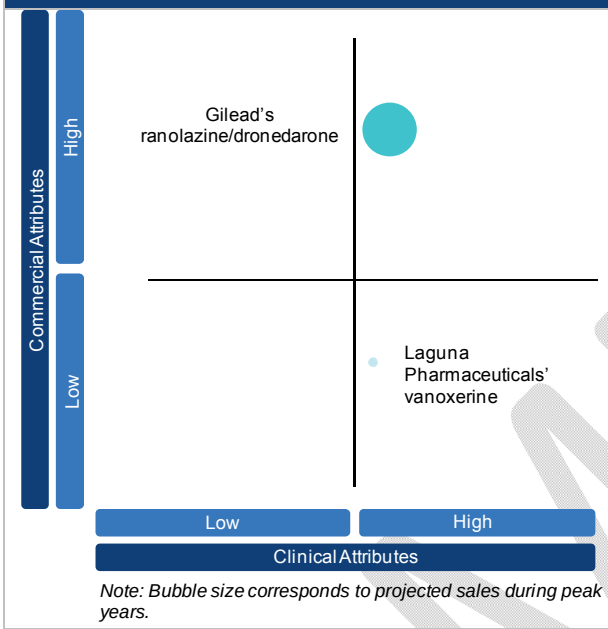
supportive clinical trial data. Even though, the Savaysa clinical trials produced solid results that confirmed its non-inferior efficacy to warfarin, and significantly reduced bleeding rates, which have become critical components for advancing a "warfarin replacement" product to market, Savaysa's future in the AF market is now uncertain. GlobalData initially believed the drug would be well positioned for those AF patients with a previous history of bleeding events, as its various dosages would allow for dose adjustments. In addition, Savaysa's convenient once-daily dosing also made it a very attractive patient option. However, the FDA's decision that Savaysa should not be used in patients with normal renal function has severely restricted the drug's patient potential. GlobalData now believes that Savaysa will struggle to capture a significant share of the anticoagulant market. With no other drug candidates presently in Phase III development for stroke prevention in AF, GlobalData does not anticipate any major developments to occur in the anticoagulant treatment landscape during the forecast period.

In terms of antiarrhythmic drugs, two drug candidates are forecast to enter the market within the next decade: Gilead's FDC of ranolazine/dronedarone and Laguna Pharmaceuticals' vanoxerine, which have both completed Phase II clinical trials. Based on the clinical trials required to bring Sanofi's Multaq (dronedarone) to market, for Gilead to gain regulatory approval for ranolazine/dronedarone, it is expected that an extensive series of Phase III clinical trials will be required to provide evidence to support its rhythm control properties and potentially superior safety profile over existing therapies. Laguna Pharmaceuticals, on the other hand, is a very small spin-off company of the pharmaceutical testing firm, ChanTest, and will require substantial outside investment in the form of venture capital or a partnership agreement, if it is to succeed in bringing its cardioversion drug candidate to market. Both drug candidates are expected to launch late in the forecast period and will not reach peak sales until after 2023.

Executive Summary

Figure below provides a competitive assessment of the late-stage pipeline agents for AF during the forecast period.

Competitive Assessment of Late-Stage Pipeline Agents for AF, 2013–2023



Note: Bubble size corresponds to projected sales during peak years.

Source: GlobalData

What Do the Physicians Think?

Key Opinion Leaders (KOLs) interviewed by GlobalData highlighted the advancement the NOACs offer in the anticoagulation of patients for stroke prevention in AF. It is expected that the continued uptake of the NOACs will be the main driver in the growth of the AF market.

"Antithrombotic drugs are certainly the most rapidly evolving field, because we have several new drugs, the NOACs, that have come or are coming into the market and they are revolutionizing the entire area."

EU Key Opinion Leader

"I think the NOACs are definitely an advance. Patients are happy that they do not have to worry about getting needle pricks, they do not have to worry about dieting restrictions, and of course, they can travel. I make sure that they understand that there is a bleeding risk, but it is not likely that there is one. In my opinion, there is more bleeding with warfarin than with the NOACs."

US Key Opinion Leader

"They are all at least as effective as vitamin K antagonists and they all are safer; this is why vitamin K antagonists should no longer be used."

EU Key Opinion Leader

"I believe the antidotes or the availability of an antidote would increase the use of NOACs. Further education of physicians will also play a good part in increasing NOAC use. So, there are lots of things which need to be done in the upcoming years to make the NOACs the number one therapy for stroke prevention. But, I do believe the drugs do have the potential for this."

EU Key Opinion Leader

Executive Summary

KOLs interviewed by GlobalData believe there is limited clinical need for NOAC antidotes, but that the significant media attention surrounding the risk of uncontrolled bleeding events and a lack of clinical knowledge about the NOACs have fueled the interest and investment in their development.

"I do think that this desire for a reversal agent is a little bit overstated, because I do think that we will end up using antidotes a lot less than people think we need to."

US Key Opinion Leader

"Antidotes are required more to reassure the physician and patient, rather than an actual unmet need in clinical practice. In fact, you don't need an antidote, that's what the big randomized clinical trials tell us."

EU Key Opinion Leader

"I think it makes sense to have an antidote. The reason that there are no antidotes was a mistaken concept from the pharma industry. They thought that these drugs would be so safe that antidotes would not be necessary. I think that most people are concerned about bleeds that will not stop and would like to have specific antidotes that will stop bleeding. I don't think there is much of a need to use such antidotes very often and it might not actually be justifiable to develop antidotes, but they are being developed because most people say they want them."

EU Key Opinion Leader

"I am not sure if antidotes will be largely used, but it's important and very necessary to have these antidotes to reassure people who are anesthesiologists, emergency doctors, and surgeons – because most of them are telling everyone that these drugs are dangerous, because there is no antidote."

EU Key Opinion Leader

KOLs interviewed by GlobalData agreed that the biggest unmet need in the management of AF is safer antiarrhythmic drugs for rhythm control; however, they state the reason for the low level of activity in the pipeline is due to the high risk involved in developing an antiarrhythmic drug. Large and costly clinical trials are required to demonstrate that a drug is safe and effective, and the track record for those antiarrhythmic drugs that have reached the market has been disappointing.

"I strongly believe that we need better antiarrhythmic drugs for rhythm control."

EU Key Opinion Leader

"Of course, for antiarrhythmic drugs, there are still unmet needs because it's clear that most [AF] patients will sometime in their lives be on antiarrhythmic drugs. But, the problem is that most companies don't want to take the risk of developing an antiarrhythmic drug because they all have been a failure."

EU Key Opinion Leader

Executive Summary

"We have had no new antiarrhythmic drugs for something like 25 years. The last one was flecainide. We had dronedarone [Multaq], but the rate of prescription of dronedarone in Europe remains very low because many countries have refused to reimburse the drug."

EU Key Opinion Leader

"To treat AF patients we could use safer rhythm control drugs, if such a thing could ever exist. We thought for a long time that dronedarone [Multaq] was the one, but it turned out that in certain groups, it will increase the risk of death. So, that did not work out."

US Key Opinion Leader

"Very few companies want to take risk of developing an antiarrhythmic drug, because that means a huge cost for development."

EU Key Opinion Leader

"It is a market which has a large number of AF patients, but it's so difficult to demonstrate something [in a clinical trial]. The problem with AF is that, of course, it's a disease with an increased risk for [shortened] life expectancy, but fortunately, the rate of complication is very low. So, if you want to demonstrate something, for example in anticoagulation, you have to make huge trials with something like 15,000 patients. So, it's a huge cost and it's too difficult to do. It's one of the main reasons why there are no new developments with antiarrhythmic drugs. And then there is still the history of dronedarone; it was a failure."

EU Key Opinion Leader

"I do think that an antiarrhythmic therapy that is very safe and very effective is needed, it's just I'm not optimistic. There has never been a drug that's been particularly effective or safe. So, if there happens to be one, I think that's great; but I don't think that there are very many people in the field who think that a new great blockbuster antiarrhythmic drug is around the corner. I don't think anyone is holding their breath."

US Key Opinion Leader

Table of Contents

1 Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

1.1 List of Tables

Table of Contents

Table of Contents

Table of Contents

Table of Contents

Table of Contents

1.2 List of Figures

Table of Contents

2 Introduction

2.1 Catalyst

Various therapeutic options are available to treat patients with atrial fibrillation (AF), and most patients will receive some form of antithrombotic therapy, a heart rate control agent, and potentially, an antiarrhythmic drug for rhythm control. All sectors of the AF market have historically been saturated with generics, with the vitamin K antagonists such as warfarin playing an important role in stroke prevention in AF. However, since 2010, and the launch of the first of the new oral anticoagulants (NOACs), a shift in the treatment of patients with AF has occurred. The NOACs offer a significant advancement in anticoagulation and their continued uptake will be the main driver of growth in the AF market over the next 10 years.

- There are now four NOACs on the market; these include Boehringer Ingelheim's Pradaxa (dabigatran), Bayer/Janssen's Xarelto (rivaroxaban), Bristol-Myers Squibb/Pfizer's Eliquis (apixaban), and Daiichi-Sankyo's Savysa (edoxaban).
- In September 2014, Daiichi-Sankyo gained label expansion in Japan for edoxaban to include the treatment of patients with AF, and it was also approved and launched in the US early in 2015 under the brand name Savaysa.
- All major treatment guidelines for the management of AF now include the NOACs as a treatment option for the anticoagulation of patients with AF, with some giving preference to the NOACs over vitamin K antagonists. Treatment guidelines also give more focus to identifying and treating patients with AF that have a low risk of stroke.
- The anticipated arrival of NOAC antidotes from 2017 onwards is also forecast to be a major driver of further NOAC uptake. The availability of NOAC antidotes is expected to ease remaining physician and patient concerns surrounding the risk of uncontrolled bleeding events.

In contrast, despite a great unmet need for safer antiarrhythmic drugs, developments in this field are expected to be much slower.

- Two potential antiarrhythmic drugs are forecast to enter the market within the next decade: Gilead's fixed-dose combination (FDC) of ranolazine and low-dose dronedarone, and Laguna Pharmaceuticals' vanoxerine, both of which have completed Phase II clinical trials. Both drug

Introduction

candidates are expected to launch late in the forecast period and will not reach peak sales until after 2023.

- The low level of activity in the pipeline is expected to continue due to the high risk involved in developing antiarrhythmic drugs.

2.2 Related Reports

- GlobalData (2014). Acute Coronary Syndrome − Global Drug Forecast and Market Analysis to 2023, July 2014, GDHC69PIDR

2.3 Upcoming Related Reports

- GlobalData (2015). Dyslipidemia − Global Drug Forecast and Market Analysis to 2023, GDHC110PIDR

Appendix

11.7 About GlobalData

GlobalData is a leading global provider of business intelligence in the healthcare industry. GlobalData provides its clients with up-to-date information and analysis on the latest developments in drug research, disease analysis, and clinical research and development. Our integrated business intelligence solutions include a range of interactive online databases, analytical tools, reports, and forecasts. Our analysis is supported by a 24/7 client support and analyst team.

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