



**GlobalData»**  
OpportunityAnalyzer

**OPIOID-INDUCED CONSTIPATION -  
OPPORTUNITY ANALYSIS AND FORECASTS TO 2017**

## Executive Summary

The table below presents the key metrics for opioid-induced constipation (OIC) in the six major pharmaceutical markets covered in this report (US, France, Germany, Italy, Spain, UK) during the forecast period from 2012–2017.

| OIC: Key Metrics in Six Major Pharmaceutical Markets, 2012–2017                                                                                   |                 |
|---------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| 2012 Patient Population Potential                                                                                                                 |                 |
| Number of Cases of Opioid-Induced Constipation                                                                                                    | 5,878,257       |
| 2012 Market Sales                                                                                                                                 |                 |
| US                                                                                                                                                | \$69.0m         |
| 5EU                                                                                                                                               | \$75.4m         |
| <b>Total</b>                                                                                                                                      | <b>\$144.4m</b> |
| Key Events (2012–2017)                                                                                                                            | Level of Impact |
| Launch of Amitiza in all EU markets in 2014                                                                                                       | ↑↑              |
| Approval of naloxegol in the US in 2014; EU in 2015                                                                                               | ↑↑              |
| Approval of bevenopran in the US in 2016; EU in 2017                                                                                              | ↑↑↑             |
| Approval of oral Relistor in the US in 2014; EU in 2015/2016                                                                                      | ↑↑↑             |
| Approval of Linzess in the US in 2016; EU in 2017                                                                                                 | ↑↑              |
| 2017 Patient Population Potential                                                                                                                 |                 |
| Number of Chronic Opioid Users                                                                                                                    | 15,921,077      |
| Total Prescription Drug-Treated Population (45%)                                                                                                  | 1,810,755       |
| 2017 Market Sales                                                                                                                                 |                 |
| US                                                                                                                                                | \$1.79bn        |
| 5EU                                                                                                                                               | \$197.6m        |
| <b>Total</b>                                                                                                                                      | <b>\$1.99bn</b> |
| Source: GlobalData.<br>For the purposes of this report, the six major pharmaceutical markets = US and 5EU (France, Germany, Italy, Spain, and UK) |                 |

### Rapid Growth in the Opioid-Induced Constipation Market is Expected from 2012 to 2017

GlobalData estimates the 2012 sales for opioid-induced constipation (OIC) to be approximately \$144.42m across the six major pharmaceutical markets covered in this forecast: the US, France, Germany, Italy, Spain, and the UK. The EU contributed the majority of these sales, with the region generating an estimated \$75.4m. In particular, Germany was the largest market, with an estimated \$41.5m in sales in 2012. By the end of the forecast period, OIC sales will grow to approximately \$1.98 billion, at a compound annual growth rate (CAGR) of 31.9% over the five-year period. The majority of sales will come from the US, which will represent more than 90% of the market (based on 6MM) in 2017.

Major drivers to the growth of the OIC market over the forecast period will include:

- The introduction of several highly targeted, oral, peripherally acting mu-opioid receptor antagonist (PAMORA) therapies, which are easily administrated with convenient dosing: AstraZeneca's naloxegol, Cubist's bevenopran and Salix's oral Relistor.
- The launch of Amitiza across the EU and the approval of Linzess across the 6MM for OIC, which will increase physician and patient awareness of non-laxative prescription options to treat constipation.

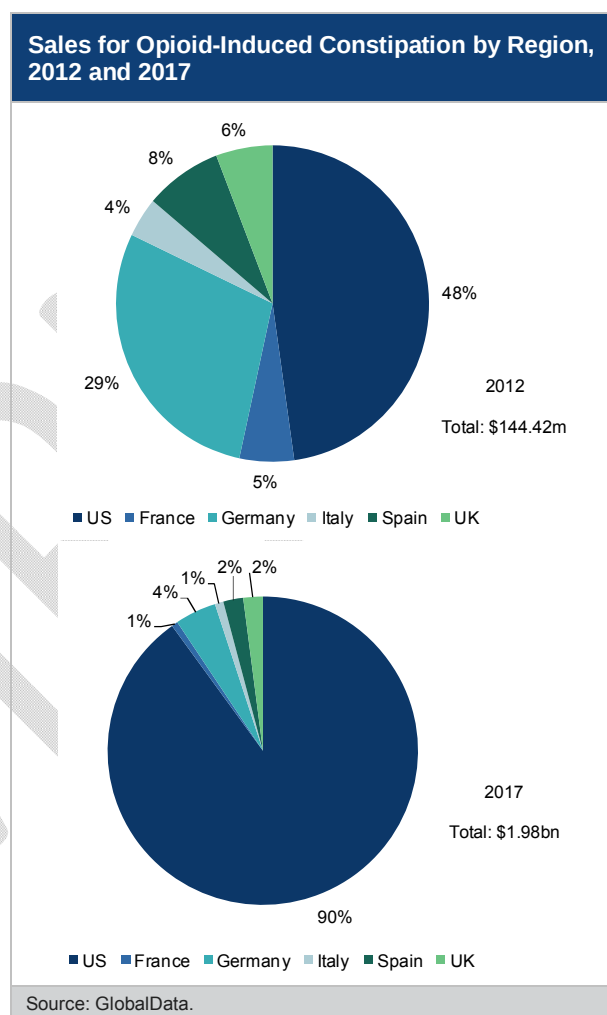
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- The growing number of OIC sufferers due to the overall population growth and continued use of opioids in the treatment of chronic non-cancer pain.

Major barriers to the growth of the OIC market will include:

- The high price of PAMORAs compared with standard laxative therapy, which may prevent their reimbursement by local health authorities and health insurance companies.
- Patient awareness of OIC. This includes the underlying difference between OIC and functional constipation, and awareness of non-laxative OIC prescription therapies. A further barrier to treating OIC is patients' reluctance to report constipation symptoms to physicians.
- Physician awareness of OIC and the resulting impact on pain management and QOL, including follow-up questions and treatment for refractory patients with non-laxative prescription drugs, which represent a barrier for OIC treatment.

The figure below illustrates the OIC sales for the six major markets during the forecast period.



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### **Aligned R&D Strategies Are Imperative for Attaining Access to a Lucrative and Underserved OIC Market**

OIC remains a hugely untapped market with little competition in the pharmaceutical arena, with the first pharmacological treatment only becoming licensed in 2008. As of September 2013, there are currently only two EU- and FDA-approved treatments available. The OIC market has a commercially attractive patient population size (more than half a million patients in the US and 5EU), as well as the scope for companies to seek accelerated approval, enabling a potentially faster and more cost-effective R&D program. As this is a new and rapidly forming market that has yet to be fully established, aligned R&D strategies are indispensable for admittance into a previously unpenetrated market.

### **Demonstrating High Efficacy while Proving No Reduction of Analgesia or Major Cardiovascular Adverse Effects is Essential**

According to key opinion leaders (KOLs) interviewed by GlobalData, the key attribute for companies wanting to establish themselves in the OIC therapeutic arena is to utilize understanding of the disease mechanism to generate safe therapies with a low side-effect profile. This will include designing clinical trial safety endpoints that adequately satisfy approval bodies. Future R&D strategies need to develop therapies using the fundamental understanding of OIC by investing in research, which in turn will be imperative for

discovering a long-term efficacious drug with a lack of undesirable side effects.

### **Corporate Strategies Include Label Expansion of Approved Constipation Drugs into OIC**

Other corporate trends include expanding the label indication for functional constipation drugs into OIC to maximize sales from this lucrative market. The decision by the FDA in April 2013 to approve Amitiza for a third indication has led companies currently developing constipation drugs to consider commencing clinical trials in patients with OIC. Ironwood has expressed interest in pursuing a label expansion into OIC for its constipation drug Linzess, and it is likely that other companies will follow suit.

### **Extensive Marketing of OIC Prescriptions Drugs is Required to Convert Patients from OTC Laxatives**

A common strategy being undertaken by companies in the OIC space is to enter partnerships and acquisitions in a bid for companies to broaden their pipeline portfolio. Examples include the acquisitions of Adolor Corporation by Cubist Pharmaceuticals and the licensing of naloxegol to AstraZeneca by Nektar. With the vast majority of novel therapeutic agents for OIC being developed by small to medium-sized pharmaceutical and biotechnology companies, GlobalData anticipates that licensing activity and the formation of new partnerships with companies possessing strong GI sales experience will be key

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in competing in a soon-to-be-congested market populated by many me-too drugs.

Besides the advent of efficacious drugs, improving diagnosis and increasing the awareness of new treatments is a key unmet need essential in increasing the drug-treatment rate for OIC. The current OIC therapeutic market is dominated by inexpensive, widely available laxatives. Despite a lack of strong evidence and poor clinical efficacy, they are currently broadly accepted as the mainstay of constipation relief. The success of prescription OIC therapies compared with that of OTC laxatives will depend on extensive marketing. Such marketing must serve to increase both patient and physician awareness of the non-laxative prescription options when treating constipation, in particular for OIC.

### **A Highly Efficacious, Approved Therapy is the Most Pressing Need in OIC**

The level of unmet need for OIC, both environmentally and clinically, is high. Key opinion leaders (KOLs) interviewed by GlobalData highlight that there is an unprecedented need for an efficacious drug for OIC treatment. Such a drug must be targeted to the cause of OIC and can only be identified following future advancements based on further critical understanding of the etiology and pathophysiology of the disease.

### **Oral PAMORAs Set to Change the OIC Treatment Landscape**

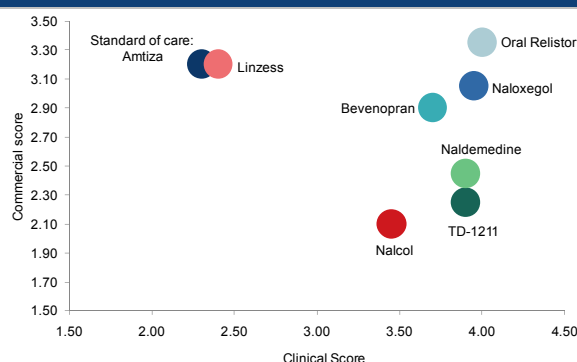
The new class of oral PAMORAs being developed is highly targeted, and KOLs interviewed by GlobalData are eagerly anticipating this class of drug. There are currently five drugs in this class in late-stage clinical development, and all represent targeted, efficacious potential treatments for OIC. However, potential regulatory hurdles remain due to doubts over major adverse cardiovascular events (MACE) associated with PAMORAs. The FDA is currently convening a body of experts to assess the drug class and provide guidance regarding the necessary clinical trials to sufficiently demonstrate safety. If approvals go ahead, the currently underserved OIC market is set to become very congested and competitive. Demonstrating superior efficacy, competitive pricing and good marketing will be crucial in gaining market share.

Over the next five years, the OIC market is expected to see significant changes. With the approval of three PAMORAs, there will be a shift in the way that drugs for OIC are prescribed. Although laxatives are likely to remain the first-line therapy, the advent of novel targeted oral therapies, alongside improved and timely diagnosis and improved physician awareness, will increase the number of patients receiving non-laxative prescription treatments.

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GlobalData assessed promising pipeline candidates both clinically and commercially, based on the opinions generated from interviews with KOLs. As illustrated in the figure below, Salix's oral Relistor emerged as the drug with the greatest future interest. This is mainly due to the substantial efficacy offered by this class of drug (PAMORA); its current commercial positioning in the OIC market, as the subcutaneous formulation is approved globally and is marketed by an industry-leading GI specialist; and its convenient as-needed oral dosage. Two competing PAMORAs, AstraZeneca's naloxegol and Cubist's bevenopran, also have very similar clinical and commercial attributes, placing them in direct competition in this soon-to-be congested market. Other players will include Theravance's TD-1211, Shionogi's naldemedine, and S.L.A. Pharmaceuticals' Nalcol, all of which will require licensing partners for successful approval and/or launch. Already marketed constipation therapies, namely Sucampo's Amitiza and Ironwood's Linzess, are expected to have an easier route to approval; however, their indirect MOA reduces their efficacy as assessed by the current measures of OIC relief. Therefore, cost-effectiveness will be difficult to prove and may result in challenges in terms of reimbursement.

**Competitive Assessment of Late-Stage Pipeline Agents in Opioid-Induced Constipation, 2012–2017**



Source: GlobalData.

### What do the Physicians Think?

The Key Opinion Leaders (KOLs) interviewed for this report highlighted a fundamental issue regarding OIC treatment and diagnosis: patients' reluctance to report the condition.

*'Most of them are very reluctant to talk about [constipation]. Often what they do when they are going to the pharmacy to pick up other products they ask the pharmacist for suggestions for something that is over-the-counter. So unless it's really, really desperate they do not want to talk to the physician about it.'*

US KOL, May 2013

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KOLs discussed the challenges when treating patients with OIC using the current standard of care.

*'The laxative-first approach takes into account healthcare cost. However, if one were to approach OIC mechanistically, using an opioid antagonist as a first-line therapy seems very reasonable. Unfortunately, to date there has not been any pharmacoeconomic data to suggest the use of opioid antagonists is cost neutral or cost reductive; this would be most helpful data to have available.'*

US KOL, July 2013

*'[First,] patients often specifically don't like lactulose, it is not always something patients really like, and second, they do not always work. I would say about half of the patients [find laxatives ineffective].'*

EU KOL, May 2013

KOLs cite the significant unmet needs for managing OIC and the remaining market opportunities.

*'There is no universally accepted definition of opioid-induced constipation and I think that is problematic in a lot of ways. The [current] definitions we have are based on two things, firstly clinical research trials which have come up with definitions for the trial, and secondly from functional constipation.'*

US KOL, June 2013

*'I think there needs to be an in-depth review of literature, looking at all the current treatments for functional constipation and how they could be used in the opioid-induced constipation. And then a consensus on how would we approach constipation, based on the data in the literature, based on the ideal world versus the practical world, and come up with a consensus statement on that.'*

US KOL, June 2013

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Even for the highly targeted therapies due to launch in the near future, uptake will hinge on physician awareness regarding the diagnosis and treatment options for OIC.

*'I work in a busy cancer center and I prescribed methylnaltrexone [Relistor] the other day and I was shocked when a registrar, who you would think would know the literature, had never even heard of it. So I think there is definitely a problem with not educating junior doctors and possibly even GPs about [pharmacological OIC treatments].'*

EU KOL, June 2013

There are currently several drugs in the pipeline with very similar mechanisms of action; the future will be brightest for companies able to differentiate their products by creating brand awareness and for products with superior side-effect profiles.

*'There are eight to nine [new drugs] that are possibly going to be in the market for opioid-induced constipation, so it's a very congested market, a very competitive market. How are [drug developers] going to compete with the first kids on the block? I mean, it's a great drug, but unfortunately, when they started developing these drugs, it was a much different time, and if it is the third, fourth, fifth player on the block, I think you are going to have a real tough time marketing your products unless you can start looking at other side effects. I have told companies that.'*

US KOL, June 2013

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## Introduction

## 2 Introduction

### 2.1 Catalyst

Opioid-induced constipation (OIC) is a new and rapidly establishing market. Due to the relaxation of regulations regarding opioid treatment, particularly in the chronic non-cancer-pain population, opioid use has risen sharply in the last 15 years. Concurrently, there has been a rapid increase in patients experiencing OIC, with approximately 40%–50% of chronic opioid users reporting symptoms. Traditionally, constipation has been treated with laxatives, based on empirical research. However, the efficacy of laxatives to treat OIC is relatively poor, and only provides adequate relief for approximately 50% of patients. Prior to 2008, the OIC market was desolate, with no approved pharmaceutical (non-laxative) treatment for this condition. There is currently a paucity of approved products, with heavy restrictions limiting their use for the majority of OIC sufferers. However, the OIC therapeutic market is set to enter an explosive period of growth over the five-year forecast period. This advance is catalyzed by a major shift in the OIC treatment algorithm with the entry of several highly targeted, efficacious, orally formulated drugs. The competitive landscape will continue to evolve over the forecast period.

*Due to the relaxation of regulations regarding opioid treatment, particularly in the chronic non-cancer pain population, opioid use has risen sharply in the last 15 years*

The major unmet need in the OIC market is a lack of efficacious drugs that targets the direct cause of OIC, agonism of mu receptors by exogenous opioids in the gut, disrupting normal motility, without causing a loss of analgesia or inducing adverse effects. This need has been addressed by promising late-stage pipeline products that directly antagonize mu receptors in the lining of the GI tract while chemical modifications restrict its systemic availability, thus preventing the molecule from crossing the blood-brain barrier. The safety and efficacy profiles of these products, once tested in clinical practice, will ultimately determine their clinical position in the future treatment landscape. Marketing and physician awareness of new OIC treatments will increase the non-laxative prescription drug-treatment rate. Within the five-year forecast period, the following drugs will be launched in the global OIC market:

- Sucampo's Amitiza, with approval in the UK anticipated in Q4 2013, 4EU in H2 2014
- AstraZeneca's naloxegol, with approval in the US anticipated in Q3 2014, UK in Q2 2015, and 4EU in Q4 2015
- Salix's oral Relistor, with approval in the US anticipated in Q4 2014, UK in Q3 2015, and 4EU in Q1 2016

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- Cubist's bevenopran, with approval in the US anticipated in Q2 2016, UK in Q1 2017, and 4EU in Q3 2017
- Ironwood's Linzess, with approval in the US anticipated in Q2 2016, UK in Q1 2017, and 4EU in Q3 2017

## Appendix

### 10.7 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. GlobalData has offices in New York, Boston, London, India, and Singapore.

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