Executive Summary

Table below presents the key metrics for insomnia in the seven major pharmaceutical markets (7MM) (US, France, Germany, Italy, Spain, UK, and Japan) during the forecast period from 2013–2023.

### Insomnia: Key Metrics in Seven Major Pharmaceutical Markets

<table>
<thead>
<tr>
<th>2013 Epidemiology</th>
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<tbody>
<tr>
<td>Prevalent Population</td>
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<tr>
<td>Treated Population</td>
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<thead>
<tr>
<th>2013 Market Sales</th>
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<tbody>
<tr>
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<tr>
<td>5EU</td>
<td>$210.9m</td>
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<tr>
<td>Japan</td>
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</tr>
<tr>
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<td>Number of first-in-class drugs</td>
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<table>
<thead>
<tr>
<th>Most Promising Pipeline Drugs</th>
<th>Peak-Year Sales</th>
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</thead>
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<tr>
<td>E-2006 (Eisai)</td>
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<table>
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<th>Key events (2013–2023)</th>
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<tbody>
<tr>
<td>Sunovion/Dainippon Sumitomo’s Lunesta (eszopiclone) patent expiry</td>
<td>↓↓↓</td>
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<tr>
<td>Merck &amp; Co.’s Belsomra launch</td>
<td>↑↑↑</td>
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<tr>
<td>Eisai’s E-2006 launch (expected)</td>
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<td>Neurim’s Circadin patent expiry</td>
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<tr>
<th>2023 Market Sales</th>
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<td>5EU</td>
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<td>Japan</td>
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</tr>
<tr>
<td>Total</td>
<td>$1,769.1m</td>
</tr>
</tbody>
</table>

Source: GlobalData

5EU = France, Germany, Italy, Spain, UK

Decline Expected in the Insomnia Market from 2013 to 2023

GlobalData estimates that sales for the insomnia drugs covered in this report were approximately $2.1 billion in 2013 across the 7MM. By the end of the forecast period in 2023, sales are expected to have declined to approximately $1.8 billion with a negative Compound Annual Growth Rate (CAGR) of 1.55%. GlobalData forecasts that sales for insomnia will steeply decline between 2013 and 2016 to $1.4 billion, primarily due to the generic erosion of Sunovion/Dainippon Sumitomo’s Lunesta (eszopiclone) in the US. Market growth is expected to occur from 2017 onwards, which can be attributed to the launch of two products, Merck & Co.’s Belsomra and Eisai’s E-2006, and an increase in the prevalent cases of insomnia.

The US dominated the 2013 base year market in terms of country-specific sales, with an estimated $1.5 billion share, which represents 71.4% of the insomnia market. GlobalData believes the US will retain its position as the largest insomnia market throughout the forecast period, ending with $1.1 billion in sales for insomnia in 2023, representing 60.8% of the global market. The US is expected to be the only market to experience a decline in sales over the 10 year forecast, with a negative CAGR of 3.13%. This decline is largely a result of Lunesta’s patent expiry in 2014 and the increased competition causing a decline in the price of extended-release zolpidem generics.
Executive Summary

The main drivers of growth of the insomnia market over the forecast period are:

- The launch of two orexin receptor antagonists, Merck & Co.’s Belsomra and Eisai’s E-2006
- An increase in prevalent cases of insomnia

The main barriers to growth of the insomnia market over the forecast period are:

- Low compliance rates for insomnia treatment
- Low diagnosis rates for insomnia
- Generic erosion of Sunovion/Dainippon Sumitomo’s Lunesta
- Generic erosion of Neurim’s Circadin (melatonin)

Figure below presents the sales for insomnia by region in the 7MM in 2013 and 2023.

Sales for Insomnia by Region, 2013–2023

<table>
<thead>
<tr>
<th>Region</th>
<th>2013 Sales</th>
<th>2023 Sales</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>$380.4m</td>
<td>$432.4m</td>
</tr>
<tr>
<td>France</td>
<td>$28.6m</td>
<td>$33.5m</td>
</tr>
<tr>
<td>Germany</td>
<td>$29.8m</td>
<td>$31.6m</td>
</tr>
<tr>
<td>Italy</td>
<td>$53.7m</td>
<td>$67.0m</td>
</tr>
<tr>
<td>Spain</td>
<td>$47.1m</td>
<td>$56.6m</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>$51.6m</td>
<td>$72.9m</td>
</tr>
<tr>
<td>Japan</td>
<td>$72.9m</td>
<td>$1,075.1m</td>
</tr>
</tbody>
</table>

Total: $2.1 billion in 2013, $1.8 billion in 2023

Source: GlobalData
R&D and Corporate Strategies within the Insomnia Market

The corporate strategy for many of the key players has been to deprioritize the insomnia market, as it is crowded and widely genericized. In the past, Sanofi, Pfizer, and Sunovion/Dainippon Sumitomo have held a majority share of the market as the marketing companies behind the first-line nonbenzodiazepines and benzodiazepines. However, their key brands now face extensive generic competition and the companies do not have any pipeline candidates to offset the decline in sales. Various research and development (R&D) and corporate strategies have been employed by players in order to compete effectively in the crowded insomnia market. These strategies include the development of products with new mechanisms of action, reformulation of generically available drugs, and strategic partnerships between companies.

Merck & Co.’s Belsomra and Eisai’s E-2006 are examples of players focusing on the development of a novel drug class for insomnia — in this case, the orexin receptor antagonists. The two companies are aiming for these drugs to have the required efficacy and safety to compete with the nonbenzodiazepines. In addition, the orexin receptor antagonists are expected to address some of the unmet needs that exist in the insomnia market, enabling these future players to differentiate their products from available treatments and gain market share.

Some smaller players in the insomnia market have focused on novel administration routes for generically available drugs as a strategy for competing in this market. Examples include Purdue’s Intermezzo (sublingual zolpidem tartrate), ECR’s Zolpimist (oral spray zolpidem tartrate), Meda’s Edluar (sublingual zolpidem tartrate), and Pernix’s Silenor (doxepin). This approach has the advantage of lower developmental costs and reduced regulatory requirements through the US Food and Drug Administration’s (FDA) 505(b)(2) process. However, these drugs have generated disappointing sales as their high cost cannot be justified by their respective clinical advantages.

It is a common corporate strategy within insomnia for companies to enter into licensing agreements for the development and marketing of insomnia products. One approach is for larger companies to acquire the global rights for a late-stage pipeline asset from a smaller company that may lack the resources to launch the candidate. Alternatively, a company may acquire the marketing rights for a brand in a certain territory. These strategies enable companies to combine efforts and resources, share ongoing R&D and marketing costs, leverage specific geographical experience, and maximize the commercial potential of a product in the crowded insomnia market.
Executive Summary

Current Treatments Leave a High Level of Unmet Need in the Insomnia Market

GlobalData has identified five unmet needs within the insomnia market:

- Products with improved safety profiles
- Products that can be used for long-term therapy in Europe
- Improved accessibility to Cognitive Behavioral Therapy (CBT) for insomnia
- Sleep medicine education for primary care physicians
- Products that improve sleep quality

The current insomnia treatment landscape is crowded with drugs that are highly efficacious in providing short-term relief of symptoms by improving sleep onset and duration. However, the principal unmet need is for drugs with improved safety profiles, as the current first-line therapies are associated with various side effects, including next-day sedation and potential for abuse.

Secondly, there is a need for drugs that can be used for long-term therapy, in Europe as the current insomnia treatments are only approved for short-term use (up to four weeks). It is widely accepted that CBT is the most effective long-term treatment for primary insomnia, as patients can apply the skills on their own in order to prevent symptom relapse. There is a need for improved CBT availability as, currently, patient access is limited by a shortage in healthcare professionals certified to deliver behavioral therapy for insomnia, and a lack of reimbursement by payers. Key Opinion Leaders (KOLs) believe there is a need for sleep medicine education for primary care physicians, as many are unaware of the treatment and referral processes available for insomnia patients. Finally, it is apparent that the current marketed and pipeline therapies do not manipulate sleep architecture in order to improve sleep quality. Hence, there is an unmet need for drugs with this approach to treatment, as enhancing Slow Wave Sleep (SWS) may reduce some of the behavioral, psychological, and physiologic effects of restricted sleep.
Executive Summary

Opportunities Remain for Products That Will Fulfill Significant Unmet Needs in the Insomnia Market

Considerable opportunity remains for products that target the unmet needs in the insomnia market. Drugs with comparable efficacy and improved long-term safety would hold a competitive advantage over current first-line therapies and would enable them to gain a large share of the market. Similarly, drugs that improve sleep quality by augmenting SWS would be viewed favorably by physicians. Drug developers should also focus on demonstrating synergy between pharmacotherapy and CBT for insomnia, in addition to utilizing sponsored Continued Medical Education (CME), both of which will improve the overall management of insomnia and drive uptake for novel products.

The Orexin Receptor Antagonists Will Be a Key Driver in the Insomnia Market

GlobalData anticipates that the launch of two products, Merck & Co.’s Belsomra and Eisai’s E-2006, will drive growth during the forecast period. Belsomra and E-2006 are orexin receptor antagonists intended as a treatment for primary insomnia. The safety profiles of drugs in this novel class are postulated to be superior to that of the nonbenzodiazepines, based on the fact that the orexins selectively promote wakefulness in contrast to the varied functions of the gamma-aminobutyric acid type A (GABA_A) receptors. Consequently, Belsomra and E-2006 are expected to address some of the unmet needs in the insomnia market and will compete directly with the nonbenzodiazepines as first-line therapies. Belsomra became the first-in-class orexin receptor antagonist following its launch in Japan in November 2014. The drug has since launched in the US in February 2015 and GlobalData believes it will become available in the 5EU in Q1 2016. E-2006 is anticipated to launch in the US during Q4 2017 and, as the second-in-class drug, it will need to demonstrate a clinical or commercial advantage over Belsomra in order to gain a notable share of the market.

GlobalData forecasts that theses novel products could drive combined sales of approximately $704.9m by 2023 in the 7MM. The most promising agent is expected to be Belsomra, due to its first-in-class status and its potential to address some of the unmet needs in the insomnia market. GlobalData forecasts that Belsomra could generate global sales of approximately $458.6m by 2023.
Executive Summary

Competitive Assessment of Orexin Receptor Antagonists in Insomnia, 2013–2023

<table>
<thead>
<tr>
<th>Commercial Attributes</th>
<th>Clinical Attributes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

Merck & Co.’s Belsomra
Eisai’s E-2006

Note: Bubble size represents approximate peak year sales of the pipeline drug.
Source: GlobalData

What do the physicians think?

Expectations are high for Belsomra, which is expected to compete as a first-line therapy for insomnia.

“I think it’s a very nice drug… I think that the results for suvorexant [are] impressive in terms of sleep latency, sleep maintenance, and daytime performance. I think it’s nice to have a new compound with [a] completely different mechanism of action on the market.”

OUS Key Opinion Leader

“[Belsomra] should be, could be the first line treatment for patients having difficulty initiating and maintaining sleep.”

OUS Key Opinion Leader

“I’m actually looking forward to having [Belsomra] available and getting clinical experience with it. I’d be likely to use it with a lot of patients.”

US Key Opinion Leader

KOLs believe that Sanofi’s Ambien (zolpidem) is the gold-standard treatment for insomnia based on its efficacy, safety, and duration of action.

“If you dose zolpidem in the proper way everybody will sleep.”

OUS Key Opinion Leader

“[Zolpidem is] the Goldilocks, not too long, not too short and is pretty well tolerated by most people.”

US Key Opinion Leader

“I might start more patients with low-dose zolpidem rather than low-dose Lunesta for the sole reason that I think maybe there’ll be more successes with low-dose zolpidem than with low-dose Lunesta.”

US Key Opinion Leader

“Zolpidem for most people I believe seems to have a bit more of a punch to help people get off to sleep.”

US Key Opinion Leader
Executive Summary

“If I need to make a choice, I do prefer zolpidem, so Stilnox, because the short half-life is best to have a good vigilance and good performance during the day because there is less residual effect during the day compared to zopiclone.”

OUS Key Opinion Leader

The most pressing unmet need in the insomnia market is for the development of drugs with improved safety, according to the physicians interviewed by GlobalData.

“I think the greatest unmet need is continued search for a... mechanism different from a benzodiazepine receptor agonist that's ideally not a controlled substance, with no potential for abuse or little potential for abuse, that has efficacy that's comparable to a benzodiazepine receptor agonist.”

US Key Opinion Leader

“There is a need for pharmacological agents that can be used for insomnia over the long term. These agents have to produce the effect with very low or non-toxicity. These drugs should be ideally working through a non-benzodiazepine mechanism, and there shouldn't be any tolerance over the long term. Also, there should be no cognitive effects the next day.”

OUS Key Opinion Leader

“I want a drug that's going to be roughly on par with a drug like zolpidem or eszopiclone that's a good bit safer... That would be the ideal product.”

US Key Opinion Leader

The classic benzodiazepines are now used rarely for the treatment of insomnia and, instead, are reserved for the treatment of insomnia patients with high levels of anxiety.

“I rarely use classic benzodiazepines. Only patients with high anxiety levels. And then lormetazepam and temazepam are the ones I prefer.”

OUS Key Opinion Leader

“I think acute insomnia, [benzodiazepines] have a role, certainly. When there's intense anxiety or a clear reason why sleep's become so bad, you might use — GPs might use diazepam then, maybe, or probably clonazepam.”

OUS Key Opinion Leader
Executive Summary

There is a significant unmet need in Europe for drugs that can be used for the long-term treatment of chronic insomnia.

“I’m still missing a benzo-like modern agent which has a chance to be given on a daily intake and will not show any withdrawal or rebound insomnia when tapered down, say after six months or even 12 months.”

OUS Key Opinion Leader

“There is a need for pharmacological agents that can be used for insomnia over the long term.”

OUS Key Opinion Leader

“We still need drugs that can be delivered, that can be administered over longer periods of time. There is a huge percentage of the population that requires them. And once we know for sure that these drugs do not face this risk we’re going to use them as much as we are using antidepressants.”

OUS Key Opinion Leader

“The unmet need will be an acceptable drug that people are prepared to give long-term — so I think for weeks and months rather than days — to treat insomnia, and a drug that is effective.”

OUS Key Opinion Leader
# Table of Contents

1 Table of Contents ..................................................................................................................... 10

1.1 List of Tables .................................................................................................................... 18

1.2 List of Figures ................................................................................................................... 24

2 Introduction ............................................................................................................................... 27

2.1 Catalyst ............................................................................................................................. 27

2.2 Related Reports ................................................................................................................ 27

3 Disease Overview ..................................................................................................................... 28

3.1 Etiology and Pathophysiology ........................................................................................... 28

3.1.1 Etiology ......................................................................................................................... 28

3.1.2 Pathophysiology ........................................................................................................... 34

3.2 Classification ..................................................................................................................... 35

3.3 Symptoms ......................................................................................................................... 38

3.4 Prognosis .......................................................................................................................... 38

4 Epidemiology ............................................................................................................................ 40

4.1 Disease Background .......................................................................................................... 40

4.2 Risk Factors and Comorbidities ....................................................................................... 40

4.3 Global Trends ................................................................................................................... 41

4.4 Forecast Methodology ....................................................................................................... 43

4.4.1 Sources Used ................................................................................................................ 49

4.4.2 Sources Not Used ......................................................................................................... 50

4.4.3 Forecast Assumptions and Methods ............................................................................. 51
# Table of Contents

4.5 Epidemiological Forecast for Acute Insomnia (2013–2023) .................................................. 60
   4.5.1 Total Prevalent Cases of Acute Insomnia ................................................................. 60
   4.5.2 Age-Specific Total Prevalent Cases of Acute Insomnia ............................................. 62
   4.5.3 Sex-Specific Total Prevalent Cases of Acute Insomnia ............................................... 63
   4.5.4 Age-Standardized Total Prevalence of Acute Insomnia ........................................... 65

4.6 Epidemiological Forecast for Chronic Insomnia (Not Fulfilling DSM-IV Criteria) (2013–2023) ........................................................................................................................................ 66
   4.6.1 Total Prevalent Cases of Chronic Insomnia (Not Fulfilling DSM-IV Criteria) .......... 66
   4.6.2 Age-Specific Total Prevalent Cases of Chronic Insomnia (Not Fulfilling DSM-IV Criteria) ................................................................................................................................. 67
   4.6.3 Sex-Specific Total Prevalent Cases of Chronic Insomnia (Not Fulfilling DSM-IV Criteria) ................................................................................................................................. 69
   4.6.4 Age-Standardized Total Prevalent Cases of Chronic Insomnia (Not Fulfilling DSM-IV Criteria) ................................................................................................................................. 71

4.7 Epidemiological Forecast for Chronic Primary Insomnia (2013–2023) .................................. 72
   4.7.1 Total Prevalent Cases of Chronic Primary Insomnia ................................................... 72
   4.7.2 Age-Specific Total Prevalent Cases of Chronic Primary Insomnia ............................ 73
   4.7.3 Sex-Specific Total Prevalent Cases of Chronic Primary Insomnia ............................ 75
   4.7.4 Age-Standardized Total Prevalence of Chronic Primary Insomnia ............................ 77

4.8 Epidemiological Forecast for Chronic Secondary Insomnia (2013–2023) ............................ 78
   4.8.1 Total Prevalent Cases of Chronic Secondary Insomnia ............................................. 78
   4.8.2 Age-Specific Total Prevalent Cases of Chronic Secondary Insomnia ........................ 79
   4.8.3 Sex-Specific Total Prevalent Cases of Chronic Secondary Insomnia ........................ 81
   4.8.4 Age-Standardized Total Prevalence of Chronic Secondary Insomnia ..................... 83
# Table of Contents

4.9 Discussion ........................................................................................................................ 84

4.9.1 Epidemiological Forecast Insight ................................................................................... 84

4.9.2 Limitations of the Analysis ............................................................................................. 85

4.9.3 Strengths of the Analysis ............................................................................................... 86

5 Disease Management............................................................................................................... 87

5.1 Diagnosis and Treatment Overview .................................................................................. 87

5.1.1 Clinical Evaluation......................................................................................................... 87

5.1.2 Referral ......................................................................................................................... 91

5.1.3 Treatment Guidelines and Leading Prescribed Drugs ................................................... 91

5.1.4 Clinical Practice............................................................................................................. 93

5.2 US ..................................................................................................................................... 97

5.3 France ............................................................................................................................. 100

5.4 Germany ......................................................................................................................... 103

5.5 Italy ................................................................................................................................. 106

5.6 Spain .............................................................................................................................. 109

5.7 UK ................................................................................................................................... 112

5.8 Japan .............................................................................................................................. 115

6 Competitive Assessment ........................................................................................................ 119

6.1 Overview ......................................................................................................................... 119

6.2 Product Profiles — Major Brands .................................................................................. 121

6.2.1 Nonbenzodiazepines ................................................................................................. 121

6.2.2 Benzodiazepines ....................................................................................................... 160

6.2.3 Melatonin Receptor Agonists ..................................................................................... 165
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.2.4</td>
<td>Low-Dose Sedating Antidepressants</td>
<td>184</td>
</tr>
<tr>
<td>6.2.5</td>
<td>Orexin Receptor Antagonists</td>
<td>197</td>
</tr>
<tr>
<td>6.3</td>
<td>Other Therapeutic Classes</td>
<td>208</td>
</tr>
<tr>
<td>7</td>
<td>Unmet Need and Opportunity</td>
<td>209</td>
</tr>
<tr>
<td>7.1</td>
<td>Overview</td>
<td>209</td>
</tr>
<tr>
<td>7.2</td>
<td>Novel Drugs with Improved Safety Profiles</td>
<td>210</td>
</tr>
<tr>
<td>7.2.1</td>
<td>Unmet Need</td>
<td>210</td>
</tr>
<tr>
<td>7.2.2</td>
<td>Gap Analysis</td>
<td>212</td>
</tr>
<tr>
<td>7.2.3</td>
<td>Opportunity</td>
<td>213</td>
</tr>
<tr>
<td>7.3</td>
<td>Drugs That Can Be Used for Long-Term Treatment</td>
<td>213</td>
</tr>
<tr>
<td>7.3.1</td>
<td>Unmet Need</td>
<td>213</td>
</tr>
<tr>
<td>7.3.2</td>
<td>Gap Analysis</td>
<td>214</td>
</tr>
<tr>
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<td>Opportunity</td>
<td>215</td>
</tr>
<tr>
<td>7.4</td>
<td>Availability of Cognitive Behavioral Therapy</td>
<td>215</td>
</tr>
<tr>
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<td>215</td>
</tr>
<tr>
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<td>Gap Analysis</td>
<td>217</td>
</tr>
<tr>
<td>7.4.3</td>
<td>Opportunity</td>
<td>217</td>
</tr>
<tr>
<td>7.5</td>
<td>Drugs That Improve the Quality of Sleep</td>
<td>218</td>
</tr>
<tr>
<td>7.5.1</td>
<td>Unmet Need</td>
<td>218</td>
</tr>
<tr>
<td>7.5.2</td>
<td>Gap Analysis</td>
<td>219</td>
</tr>
<tr>
<td>7.5.3</td>
<td>Opportunity</td>
<td>220</td>
</tr>
<tr>
<td>7.6</td>
<td>Education for Primary Care Physicians</td>
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</tr>
<tr>
<td>7.6.1</td>
<td>Unmet Need</td>
<td>220</td>
</tr>
</tbody>
</table>
# Table of Contents

7.6.2 Gap Analysis .................................................................................................................. 221
7.6.3 Opportunity .................................................................................................................... 222

8 Pipeline Assessment ............................................................................................................. 223
  8.1 Overview ............................................................................................................................. 223
  8.2 Clinical Trial Mapping ......................................................................................................... 223
    8.2.1 Clinical Trials by Sponsor Type ................................................................................. 223
  8.3 Promising Drugs in Clinical Development ......................................................................... 224
    8.3.1 E-2006 ......................................................................................................................... 225
    8.3.2 Piromelatine ................................................................................................................. 230
  8.4 Promising Drugs in Early-Stage Development .............................................................. 235
  8.5 Other Drugs in Development ............................................................................................ 237

9 Current and Future Players .................................................................................................... 238
  9.1 Overview ............................................................................................................................. 238
  9.2 Trends in Corporate Strategy ............................................................................................ 242
  9.3 Company Profiles ............................................................................................................. 244
    9.3.1 Sanofi ........................................................................................................................... 244
    9.3.2 Sunovion/Dainippon Sumitomo .................................................................................. 247
    9.3.3 Pfizer ............................................................................................................................ 249
    9.3.4 Takeda .......................................................................................................................... 253
    9.3.5 Merck & Co. ................................................................................................................. 256
    9.3.6 Meda ............................................................................................................................. 260
    9.3.7 Eisai ............................................................................................................................. 263
    9.3.8 Purdue .......................................................................................................................... 265
Table of Contents

9.3.9 Neurim .................................................................268
9.3.10 Pernix Therapeutics ...........................................272

10 Market Outlook ........................................................275

10.1 Global Markets .......................................................275
10.1.1 Forecast ...............................................................275
10.1.2 Drivers and Barriers — Global Issues ....................279

10.2 United States ........................................................281
10.2.1 Forecast ...............................................................281
10.2.2 Key Events ..........................................................284
10.2.3 Drivers and Barriers ..............................................284

10.3 France .................................................................286
10.3.1 Forecast ...............................................................286
10.3.2 Key Events ..........................................................289
10.3.3 Drivers and Barriers ..............................................289

10.4 Germany ..............................................................291
10.4.1 Forecast ...............................................................291
10.4.2 Key Events ..........................................................294
10.4.3 Drivers and Barriers ..............................................294

10.5 Italy .................................................................296
10.5.1 Forecast ...............................................................296
10.5.2 Key Events ..........................................................299
10.5.3 Drivers and Barriers ..............................................299

10.6 Spain .................................................................300
# Table of Contents

10.6.1 Forecast ...................................................................................................................... 300
10.6.2 Key Events .................................................................................................................. 304
10.6.3 Drivers and Barriers .................................................................................................... 304
10.7 United Kingdom .............................................................................................................. 306
10.7.1 Forecast ...................................................................................................................... 306
10.7.2 Key Events .................................................................................................................. 309
10.7.3 Drivers and Barriers .................................................................................................... 309
10.8 Japan ...................................................................................................................................... 311
10.8.1 Forecast ...................................................................................................................... 311
10.8.2 Key Events .................................................................................................................. 314
10.8.3 Drivers and Barriers .................................................................................................... 314

11 Appendix................................................................................................................................. 316
11.1 Bibliography .................................................................................................................... 316
11.2 Abbreviations .................................................................................................................. 350
11.3 Methodology ................................................................................................................... 354
11.4 Forecasting Methodology ................................................................................................ 354
11.4.1 Diagnosed Insomnia Patients ...................................................................................... 354
11.4.2 Percent Drug-Treated Patients .................................................................................... 355
11.4.3 Drugs Included in Each Therapeutic Class .................................................................. 355
11.4.4 Launch and Patent Expiry Dates .................................................................................. 356
11.4.5 General Pricing Assumptions ...................................................................................... 357
11.4.6 Individual Drug Assumptions ...................................................................................... 358
11.4.7 Generic Erosion .......................................................................................................... 371
## Table of Contents

11.4.8  Pricing of Pipeline Agents .................................................................................. 372

11.5  Primary Research — KOLs Interviewed for this Report ........................................... 373

11.6  Primary Research — Prescriber Survey .................................................................. 375

11.7  About the Authors .................................................................................................. 376

11.7.1  Analyst ............................................................................................................. 376

11.7.2  Therapy Area Director ....................................................................................... 376

11.7.3  Epidemiologist .................................................................................................. 377

11.7.4  Global Head of Healthcare ................................................................................ 377

11.8  About GlobalData .................................................................................................... 378

11.9  Disclaimer .............................................................................................................. 378
1.1 List of Tables

Table 1: ICSD-2 Classification of Sleep Disorders and Subtypes of Insomnia ........................................... 29
Table 2: Comorbid Psychiatric Disorders, Medical Disorders, Medications, and Substances that Can Cause Insomnia .................................................................................................................................................. 32
Table 3: The Three Main Classifications of Insomnia Disorders ........................................................................ 36
Table 4: Symptoms of Insomnia .......................................................................................................................... 38
Table 5: Risk Factors and Comorbidities for Insomnia ....................................................................................... 41
Table 6: DSM-IV Diagnostic Criteria for Primary Insomnia ............................................................................... 44
Table 7: Sources of Epidemiological Data Used for the Forecast for Total Prevalent Cases of Acute Insomnia in the 7MM ........................................................................................................................................... 45
Table 8: Sources of Epidemiological Data Used for the Forecast for Total Prevalent Cases of Chronic Insomnia (Not Fulfilling DSM-IV Criteria) in the 7MM .......................................................................................................................... 46
Table 9: Sources of Epidemiological Data Used for the Forecast for Total Prevalent Cases of Chronic Primary Insomnia in the 7MM ........................................................................................................................................... 47
Table 10: Sources of Epidemiological Data Used for the Forecast for Total Prevalent Cases of Chronic Secondary Insomnia in the 7MM ........................................................................................................................................... 48
Table 11: 7MM, Total Prevalent Cases of Acute Insomnia, Both Sexes, Ages ≥15 Years, N, Select Years 2013–2023 ........................................................................................................................................... 61
Table 12: 7MM, Age-Specific Total Prevalent Cases of Acute Insomnia, Both Sexes, N (Row %), 2013 ........... 62
Table 13: 7MM, Sex-Specific Total Prevalent Cases of Acute Insomnia, Ages ≥15 Years, N (Row %), 2013 .. 64
Table 14: 7MM, Total Prevalent Cases of Chronic Insomnia (Not Fulfilling DSM-IV Criteria), Both Sexes, Ages ≥15 Years, N, Select Years 2013–2023 ........................................................................................................................................... 66
Table 15: 7MM, Age-Specific Total Prevalent Cases of Chronic Insomnia (Not Fulfilling DSM-IV Criteria), Both Sexes, N (Row %), 2013 ........................................................................................................................................... 68
Table 16: 7MM, Sex-Specific Total Prevalent Cases of Chronic Insomnia (Not Fulfilling DSM-IV Criteria), Ages ≥15 Years, N (Row %), 2013 ........................................................................................................................................... 70
Table 17: 7MM, Total Prevalent Cases of Chronic Primary Insomnia, Both Sexes, Ages ≥15 Years, N, Select Years 2013–2023 ................................ ................................ ................................ .......................................................... 72

Table 18: 7MM, Age-Specific Total Prevalent Cases of Chronic Primary Insomnia, Both Sexes, N (Row %), 2013 .................................................................................................................................................. 74

Table 19: 7MM, Sex-Specific Total Prevalent Cases of Chronic Primary Insomnia, Ages ≥15 Years, N (Row %), 2013 .................................................................................................................................................. 76

Table 20: 7MM, Total Prevalent Cases of Chronic Secondary Insomnia, Both Sexes, Ages ≥15 Years, N, 2013–2023 .............................................................................................................................................. 78

Table 21: 7MM, Age-Specific Total Prevalent Cases of Chronic Secondary Insomnia, Both Sexes, N (Row %), 2013 .............................................................................................................................................. 80

Table 22: 7MM, Sex-Specific Total Prevalent Cases of Chronic Secondary Insomnia, Ages ≥15 Years, N (Row %), 2013 .............................................................................................................................................. 82

Table 23: Examples of Patient Questionnaires Used in the Diagnosis of Insomnia ................................................. 89

Table 24: Treatment Guidelines for Insomnia .............................................................................................................. 92

Table 25: Most Prescribed Drugs for Insomnia by Class in the Global Markets, 2013 .......................................................... 93

Table 26: Country Profile — US .................................................................................................................................. 100

Table 27: Country Profile — France ........................................................................................................................... 103

Table 28: Country Profile — Germany ......................................................................................................................... 106

Table 29: Country Profile — Italy .................................................................................................................................. 109

Table 30: Country Profile — Spain .................................................................................................................................. 112

Table 31: Country Profile — UK .................................................................................................................................. 115

Table 32: Country Profile — Japan .................................................................................................................................. 118

Table 33: Leading Treatments for Insomnia, 2015 ........................................................................................................ 121

Table 34: Product Profile — Ambien/Ambien CR ......................................................................................................... 124

Table 35: Ambien/Ambien CR SWOT Analysis, 2015 ............................................................................................... 128

Table 36: Global Sales Forecast ($m) for Ambien, 2013–2023 ................................................................................... 129
Table of Contents

Table 37: Global Sales Forecasts ($m) for Ambien CR, 2013–2023 ................................................................. 129
Table 38: Product Profile — Intermezzo ........................................................................................................ 132
Table 39: Pivotal Trials of Intermezzo in Insomnia ......................................................................................... 133
Table 40: Intermezzo SWOT Analysis, 2015 .................................................................................................... 135
Table 41: Global Sales Forecast ($m) for Intermezzo, 2013–2023 ................................................................. 136
Table 42: Product Profile — Zolpimist ........................................................................................................... 138
Table 43: Zolpimist SWOT Analysis, 2015 .................................................................................................... 140
Table 44: Global Sales Forecast ($m) for Zolpimist, 2013–2023 ................................................................ 141
Table 45: Product Profile — Edluar ............................................................................................................... 143
Table 46: Edluar SWOT Analysis, 2015 ........................................................................................................ 145
Table 47: Global Sales Forecast ($m) for Edluar, 2013–2023 .................................................................... 146
Table 48: Product Profile — Lunesta ............................................................................................................. 148
Table 49: Adverse Events at ≥2% Incidence in Lunesta Clinical Trials ....................................................... 151
Table 50: Lunesta SWOT Analysis, 2015 ...................................................................................................... 152
Table 51: Global Sales Forecast ($m) for Lunesta, 2013–2023 .................................................................. 153
Table 52: Product Profile — Sonata ............................................................................................................. 155
Table 53: Adverse Events at ≥2% Incidence in Sonata Trials ........................................................................ 158
Table 54: Sonata SWOT Analysis, 2015 ...................................................................................................... 159
Table 55: Global Sales Forecast ($m) for Sonata, 2013–2023 .................................................................... 160
Table 56: Benzodiazepine SWOT Analysis, 2015 ....................................................................................... 164
Table 57: Global Sales Forecasts ($m) for the Benzodiazepines, 2013–2023 ............................................... 165
Table 58: Product Profile — Hetlioz ............................................................................................................. 167
Table 59: Results of a Phase III clinical trial of Hetlioz in Transient Insomnia ................................................ 168
Table 60: Results of a Phase III clinical trial of Hetlioz in Chronic Insomnia ................................................ 169
Table of Contents

Table 61: Adverse Events Observed in Clinical Trials of Hetlioz ................................................................. 170
Table 62: Hetlioz SWOT Analysis, 2015........................................................................................................... 170
Table 63: Product Profile — Rozerem ............................................................................................................ 173
Table 64: Incidence (%) of Adverse Events in Rozerem’s Clinical Trials ..................................................... 175
Table 65: Rozerem SWOT Analysis, 2015 ...................................................................................................... 176
Table 66: Global Sales Forecast ($m) for Rozerem, 2013–2023 ................................................................. 177
Table 67: Product Profile — Circadin ............................................................................................................ 179
Table 68: Frequency of Adverse Reactions Observed in Clinical Trials of Circadin ................................... 182
Table 69: Circadin SWOT Analysis, 2015 .................................................................................................... 183
Table 70: Global Sales Forecast ($m) for Circadin, 2013–2023 ............................................................... 184
Table 71: Product Profile — Silenor ............................................................................................................. 186
Table 72: Objective Sleep Efficacy Measures of Silenor in Chronic Primary Insomnia ............................... 188
Table 73: Objective Sleep Efficacy Measures of Silenor in Elderly Chronic Primary Insomnia Patients ....... 189
Table 74: Subjective Sleep Efficacy Measures of Silenor in Elderly Chronic Primary Insomnia Patients ...... 190
Table 75: Incidence (%) of Adverse Events in Silenor Trials ....................................................................... 191
Table 76: Silenor SWOT Analysis, 2015 ...................................................................................................... 191
Table 77: Global Sales Forecasts ($m) for Silenor, 2013–2023 ................................................................. 192
Table 78: Low-Dose Sedating Antidepressants SWOT Analysis, 2015 ...................................................... 196
Table 79: Global Sales Forecast ($m) for Low-Dose Sedating Antidepressants, 2013–2023 ...................... 197
Table 80: Product Profile — Belsomra .......................................................................................................... 200
Table 81: Pooled Sleep Efficacy Measures from Two Phase III Trials of Belsomra in Primary Insomnia .... 202
Table 82: Belsomra Pooled Adverse Events at ≥2% Incidence in the First 3 Months of Phase III Clinical Trials .............................................................................................................................................. 204
Table 83: Belsomra SWOT Analysis, 2015 .................................................................................................. 206
Table 84: Global Sales Forecast ($) for Belsomra, 2013–2023 ................................................................. 207
Table of Contents

Table 85: Summary of Minor Therapeutic Classes, 2015 ................................................................. 208
Table 86: Unmet Needs and Opportunities in Insomnia........................................................................ 210
Table 87: Product Profile — E-2006.................................................................................................. 226
Table 88: Sleep Efficacy Measures from a Phase I Trial of E-2006 in Primary Insomnia Patients .......... 227
Table 89: E-2006 SWOT Analysis, 2015............................................................................................ 229
Table 90: Global Sales Forecast ($) for E-2006, 2013–2023 .............................................................. 230
Table 91: Product Profile — Piromelatine............................................................................................ 232
Table 92: Piromelatine SWOT Analysis, 2015.................................................................................... 235
Table 93: Drugs in Development, 2015.............................................................................................. 237
Table 94: Key Companies in the Insomnia Market in the 7MM, 2013................................................. 240
Table 95: Sanofi’s Insomnia Portfolio Assessment, 2015................................................................. 246
Table 96: Sunovion/Dainippon Sumitomo’s Insomnia Portfolio Assessment, 2015............................ 248
Table 97: Pfizer’s Insomnia Portfolio Assessment, 2015................................................................. 252
Table 98: Takeda’s Insomnia Portfolio Assessment, 2015................................................................. 255
Table 99: Merck’s Insomnia Portfolio Assessment, 2015................................................................. 259
Table 100: Meda’s Insomnia Portfolio Assessment, 2015................................................................. 262
Table 101: Eisai’s Insomnia Portfolio Assessment, 2015................................................................. 264
Table 102: Purdue’s Insomnia Portfolio Assessment, 2015............................................................. 267
Table 103: Neurim’s Insomnia Portfolio Assessment, 2015............................................................. 271
Table 104: Pernix Therapeutics’ Insomnia Portfolio Assessment, 2015............................................. 273
Table 105: Global Sales Forecast ($m) for Insomnia, 2013–2023....................................................... 277
Table 106: Insomnia Market — Drivers and Barriers, 2013–2023..................................................... 279
Table 107: Sales Forecast ($m) for Insomnia in the United States, 2013–2023................................. 282
Table 108: Key Events Impacting Sales for Insomnia in the US, 2013–2023........................................ 284
Table of Contents

Table 109: Insomnia Market in the US — Drivers and Barriers, 2013–2023......................................................284
Table 110: Sales Forecasts ($m) for Insomnia in France, 2013–2023 .................................................................287
Table 111: Key Events Impacting Sales for Insomnia in France, 2013–2023....................................................289
Table 112: Insomnia Market in France — Drivers and Barriers, 2013–2023 .......................................................289
Table 113: Sales Forecast ($m) for Insomnia in Germany, 2013–2023 ..............................................................292
Table 114: Key Events Impacting Sales for Insomnia in Germany, 2013–2023..................................................294
Table 115: Insomnia Market in Germany — Drivers and Barriers, 2013–2023 ....................................................294
Table 116: Sales Forecast ($m) for Insomnia in Italy, 2013–2023 .................................................................297
Table 117: Key Events Impacting Sales for Insomnia in Italy, 2013–2023.......................................................299
Table 118: Insomnia Market in Italy — Drivers and Barriers, 2013–2023 .........................................................299
Table 119: Sales Forecast ($m) for Insomnia in Spain, 2013–2023 ...............................................................302
Table 120: Key Events Impacting Sales for Insomnia in Spain, 2013–2023.....................................................304
Table 121: Insomnia Market in Spain — Drivers and Barriers, 2013–2023 .......................................................304
Table 122: Sales Forecast ($m) for Insomnia in the UK, 2013–2023 .................................................................307
Table 123: Key Events Impacting Sales for Insomnia in the UK, 2013–2023 ....................................................309
Table 124: Insomnia Market in the UK — Drivers and Barriers, 2013–2023 ....................................................309
Table 125: Sales Forecast ($m) for Insomnia in Japan, 2013–2023 ...............................................................312
Table 126: Key Events Impacting Sales for Insomnia in Japan, 2013–2023....................................................314
Table 127: Insomnia Market in Japan — Drivers and Barriers, 2013–2023 ......................................................314
Table 128: Key Launch Dates .........................................................................................................................356
Table 129: Key Patent Expiries ......................................................................................................................356
Table 130: High-Prescribing Physicians (Non-KOLs) Surveyed, By Country ..................................................375
1.2 List of Figures

Figure 1: The “3P” Model of Insomnia
Figure 2: Global Average of the Total Prevalence of Insomnia Symptoms and Diagnoses
Figure 3: Patient Flow for the Epidemiological Forecast of Insomnia in the 7MM
Figure 4: 7MM, Total Prevalent Cases of Acute Insomnia, Both Sexes, Ages ≥15 Years, N, 2013–2023
Figure 5: 7MM, Age-Specific Total Prevalent Cases of Acute Insomnia, Both Sexes, N, 2013
Figure 6: 7MM, Sex-Specific Total Prevalent Cases of Acute Insomnia, Ages ≥15 Years, N, 2013
Figure 7: 7MM, Age-Standardized Total Prevalence of Acute Insomnia (%), Ages ≥15 Years, by Sex, 2013
Figure 8: 7MM, Total Prevalent Cases of Chronic Insomnia (Not Fulfilling DSM-IV Criteria), Both Sexes, Ages ≥15 Years, N, 2013–2023
Figure 9: 7MM, Age-Specific Total Prevalent Cases of Chronic Insomnia (Not Fulfilling DSM-IV Criteria), Both Sexes, N, 2013
Figure 10: 7MM, Sex-Specific Total Prevalent Cases of Chronic Insomnia (Not Fulfilling DSM-IV Criteria), Ages ≥15 Years, N, 2013
Figure 11: 7MM, Age-Standardized Total Prevalence of Chronic Insomnia (Not Fulfilling DSM-IV Criteria) (%), Ages ≥15 Years, by Sex, 2013
Figure 12: 7MM, Total Prevalent Cases of Chronic Primary Insomnia, Both Sexes, Ages ≥15 Years, N, 2013–2023
Figure 13: 7MM, Age-Specific Total Prevalent Cases of Chronic Primary Insomnia, Both Sexes, N, 2013
Figure 14: 7MM, Sex-Specific Total Prevalent Cases of Chronic Primary Insomnia, Ages ≥15 Years, N, 2013
Figure 15: 7MM, Age-Standardized Total Prevalence of Chronic Primary Insomnia (%), Ages ≥15 Years, by Sex, 2013
Figure 16: 7MM, Total Prevalent Cases of Chronic Secondary Insomnia, Both Sexes, Ages ≥15 Years, N, 2013–2023
Figure 17: 7MM, Age-Specific Total Prevalent Cases of Chronic Secondary Insomnia, Both Sexes, N, 2013
Table of Contents

Figure 18: 7MM, Sex-Specific Total Prevalent Cases of Chronic Secondary Insomnia, Ages ≥15 Years, N, 2013 ................................................................. 82

Figure 19: 7MM, Age-Standardized Total Prevalence of Chronic Secondary Insomnia (%), Ages ≥15 Years, by Sex, 2013 ................................................................. 83

Figure 20: Insomnia Diagnosis Algorithm ................................................................. 88

Figure 21: Chronic Insomnia Treatment Algorithm ................................................ 96

Figure 22: Belsomra’s Development in Insomnia ..................................................... 201

Figure 23: Insomnia Therapeutics — Sponsor Type, 2015 .................................... 224

Figure 24: Insomnia — Phase II-III Pipeline, 2015 ................................................. 225

Figure 25: Clinical and Commercial Positioning of E-2006 ..................................... 228

Figure 26: Clinical and Commercial Positioning of Piromelatine ......................... 234

Figure 27: Global Sales of Products for Insomnia by Company, 2013–2023 .......... 241

Figure 28: Company Portfolio Gap Analysis in Insomnia, 2013–2023 .................... 242

Figure 29: Sanofi SWOT Analysis in Insomnia, 2013–2023 .................................... 246

Figure 30: Sunovion/Dainippon Sumitomo SWOT Analysis in Insomnia, 2013–2023 ................................................................. 249

Figure 31: Pfizer SWOT Analysis in Insomnia, 2013–2023 ..................................... 253

Figure 32: Takeda SWOT Analysis in Insomnia, 2013–2023 .................................... 255

Figure 33: Merck SWOT Analysis in Insomnia, 2013–2023 .................................... 260

Figure 34: Meda SWOT Analysis in Insomnia, 2013–2023 ..................................... 263

Figure 35: Eisai SWOT Analysis in Insomnia, 2013–2023 ..................................... 265

Figure 36: Purdue SWOT Analysis in Insomnia, 2013–2023 ............................... 268

Figure 37: Neurim SWOT Analysis in Insomnia, 2013–2023 .................................... 271

Figure 38: Pernix Therapeutics SWOT Analysis in Insomnia, 2013–2023 ............ 274

Figure 39: Global Sales for Insomnia by Region, 2013–2023 ............................... 278

Figure 40: Sales for Insomnia in the United States by Drug Class, 2013–2023 .......... 283
Table of Contents

Figure 41: Sales for Insomnia in France by Drug Class, 2013–2023 .................................................. 288
Figure 42: Sales for Insomnia in Germany by Drug Class, 2013–2023 .............................................. 293
Figure 43: Sales for Insomnia in Italy by Drug Class, 2013–2023 .................................................. 298
Figure 44: Sales for Insomnia in Spain by Drug Class, 2013–2023 ................................................. 303
Figure 45: Sales for Insomnia in the UK by Drug Class, 2013–2023 .............................................. 308
Figure 46: Sales for Insomnia in Japan by Drug Class, 2013–2023 ................................................. 313
Introduction

2 Introduction

2.1 Catalyst

Insomnia is the most common sleep disorder and is believed to affect approximately 35% of the global population. The insomnia market is widely genericized, creating a competitive environment for new products. As such, the treatment algorithm centers on the generically available nonbenzodiazepines and low-dose sedating antidepressants, despite the launch of numerous novel agents. The value of the insomnia market is set to decline following the loss of exclusivity for Sunovion/Dainippon Sumitomo’s Lunesta, the top selling insomnia drug, in April 2014. However, GlobalData expects the launch of the orexin receptor antagonists to drive growth of the insomnia market, as they may address some of the unmet needs. The catalysts and objectives for this report are:

• To assess the current competitive landscape in light of the extensive generic competition faced by most key brands
• To evaluate the significance of late-stage pipeline products, and to show how their launch will shape the future insomnia market
• To identify the significant unmet needs in the insomnia market
• To highlight the remaining opportunities in the insomnia market
• To assess the varying approaches to treatment in the different markets of the 7MM

2.2 Related Reports

• GlobalData (2014). PharmaPoint: Major Depressive Disorder – Global Drug Forecast and Market Analysis to 2023, May 2014, GDHC85PIDR
• GlobalData (2014). PharmaPoint: Neuropathic Pain – Global Drug Forecast and Market Analysis to 2022, April 2014, GDHC70PIDR
Appendix

11.8 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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