Table below presents the key metrics for Cushing’s syndrome (CS) in the six major pharmaceutical markets (6MM) (US, France, Germany, Italy, Spain, and UK) covered in this report during the forecast period from 2013–2018.

Rapid Growth of the CS Market Is Expected from 2013 to 2018

GlobalData estimates that 2013 sales for CS were approximately $179m across the 6MM. The US contributed to the majority of these sales, generating approximately $129m in 2013. By the end of the forecast period, CS drug sales will grow to approximately $499m at a Compound Annual Growth Rate (CAGR) of 22.74% over the five-year period. The majority of these sales will continue to come from the US, representing approximately 74% of the 6MM in 2018.

Major drivers for the growth of the CS drug market will include:

- The launch of the second-generation steroidogenesis inhibitors, such as Cortendo AB’s NormoCort (COR-003) and Novartis’ LCI699 in the US. These pharmacological agents will be heralded by physicians and patients alike, who are demanding better medical treatments demonstrating superior efficacy and safety properties. These newer agents will eventually replace existing steroidogenesis inhibitors, such as ketoconazole and Metopirone (metyrapone), and will become the main stimulants for market growth towards the end of the forecast period.

- The introduction of Signifor LAR (pasireotide) in the 6MM, a long-acting release (LAR) version of Signifor (pasireotide). This new depot formulation only has to be administered
Executive Summary

once every 28 days as opposed to the drug’s predecessor, Signifor, which is prescribed twice daily.

- The arrival of HRA Pharma’s Ketoconazole HRA (ketoconazole) onto the European market in 2015. If the French drug developer secures approval for its branded generic of ketoconazole, the drug’s availability to CS sufferers will increase significantly.

- The unveiling of Corcept Therapeutics’ Korlym (mifepristone) in the European Union (EU) in 2015. Korlym is already accessible to CS sufferers in the US and GlobalData expects the medical therapy to be available to EU physicians soon, eliciting an expansion of the European CS market.

- An increase in the diagnosed prevalence of CS. This is expected due to population growth and a heightened interest in the condition from pharmaceutical companies. As current and new players advance physician education and awareness of CS, the referral speeds, time to diagnosis, volume of diagnosed CS individuals, and the number of treated patients will all improve.

Major barriers to the growth of the CS drug market will include:

- European austerity measures, which will continue to restrict healthcare spending, tempering CS drug sales. Cost-conscious healthcare authorities, principally in the five European Union countries (5EU) (France, Germany, Italy, Spain, and UK), will limit premium-pricing opportunities for new pharmacological agents.

- Difficulty in diagnosis. The non-specific symptoms of CS overlap with other, more prevalent conditions, such as hyperglycemia, obesity, and hypertension. As a result, it proves challenging for physicians in primary care to swiftly and accurately diagnose, or even suspect, CS. Consequently, patients are often left untreated for several years following their initial manifestations of the disease.

- The sparsely populated pipeline. The complex nature and lack of understanding of CS and, in particular, Cushing’s disease, continues to hinder the development of efficacious, safe, and tolerable agents.

- The low cost of drugs, such as ketoconazole, Metopirone (metyrapone), and Lysodren (mitotane). This will retard growth in the CS marketplace, as it presents a stiff barrier to the entry of novel, more expensive, agents.
Executive Summary

Figure below illustrates the expected sales for CS medications in the US and the 5EU (6MM) during the forecast period.

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Sales</th>
<th>Percentage of US Sales</th>
<th>Percentage of EU Sales</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>$179m</td>
<td>28%</td>
<td>72%</td>
</tr>
<tr>
<td>2018</td>
<td>$499m</td>
<td>26%</td>
<td>74%</td>
</tr>
</tbody>
</table>

High Unmet Need for Cushing’s Syndrome Drugs Expected to Facilitate Rapid Uptake of Pipeline Agents

GlobalData has meticulously evaluated the overall level of unmet need within the CS marketplace, deducing it to be quite high. It was unanimously agreed upon by Key Opinion Leaders (KOLs) interviewed by GlobalData that there is an absence of efficacious and safe pharmacological therapies targeting the root cause of Cushing’s disease. Signifor (pasireotide) is the only approved drug on the market whose mechanism of action achieves such a feat, but its limiting efficacy and a worrying side effect profile have not made it a firm favorite among prescribing physicians. As a result, experts disclosed that CS drug developers should concentrate their research and development (R&D) resources on broadening their understanding of the disease pathophysiology. Generally speaking, KOLs are searching for medications that possess positive safety and efficacy characteristics, namely for patients suffering from severe cortisol hypersecretion. Several marketed treatments, such as ketoconazole and Metopirone (metyrapone), display diminishing efficacy over time and are associated with a plethora of adverse events.

GlobalData believes that these high levels of unmet needs for drugs with positive safety and efficacy characteristics and for medicines that are directed against the source of Cushing’s disease will not be completely addressed by the end of the forecast period. Come 2018, the CS drug
Executive Summary

landscape will be in the nascent stages of a significant transformation with the arrival of Novartis’ LCI699 and Cortendo AB’s NormoCort (COR-003) providing relief to some of these concerns. Price permitting, GlobalData is confident that these two next-generation steroidogenesis inhibitors will rapidly become incorporated into physicians’ treatment algorithms. However, GlobalData feels that the introduction of Signifor LAR (pasireotide) will do little to satisfy physicians’ growing requests for safe and effective drugs directed against the underlying cause of Cushing’s disease (the pituitary tumor). Consequently, this unmet need will remain outstanding at the end of the forecast period. To conclude, it is clearly evident that lucrative opportunities exist for current and future players to exploit with regard to the way CS patients are managed.

Steroidogenesis Inhibitors Are Expected to Dominate the Cushing’s Syndrome Marketplace by 2018

GlobalData is certain that steroidogenesis inhibitors will rule the marketplace by the end of the forecast period, as the CS drug pipeline is fairly limited in terms of drugs with diverse mechanisms of action. KOLs are apprehensive about the safety of existing steroidogenesis inhibitors (ketoconazole and Metopirone [metyrapone]) and the compensatory rise in adrenocorticotropic hormone (ACTH) levels elicited by them. This rise in ACTH levels leads to an escape phenomenon and waning drug efficacy. Despite these concerns, the late-stage pipeline for CS drugs is comprised of agents blocking enzyme activity and cortisol synthesis (LCI699 and NormoCort [COR-003]). These newer entrants operate akin to the more mature steroidogenesis inhibitors, ketoconazole and Metopirone, but exhibit greater safety and efficacy, have more convenient dosing regimens, and have been evaluated in clinical trial settings. Signifor LAR (pasireotide), a simple reformulation of the currently marketed Signifor (pasireotide), again, lacks uniqueness, and is the only medication outside of the steroidogenesis drug class that is projected to enter the CS market within the five-year forecast period.

Despite the fact that steroidogenesis inhibitors only act at the level of the adrenal glands, GlobalData projects that this class will be responsible for approximately 49% of CS drug sales in the 6MM in 2018, climbing from 28% in 2013. This will be partly due to the introduction of expensive, premium-priced enzyme-blocking drugs, such as Novartis’ LCI699 and Cortendo AB’s NormoCort, during the forecast period. Novartis has the global capacity and brand power to market its product quite extensively which, in turn, will strengthen physician awareness of CS. For that reason, the number of diagnosed prevalence cases of CS will increase, augmenting the condition’s market size. Additionally, the fact that generic ketoconazole is cost-effective and its branded version, HRA Pharma’s Ketoconazole HRA, will soon receive approval for CS in the European market, will
Executive Summary

further explain the growth in revenue of the steroidogenesis inhibitors. Early-stage drugs, such as ones being developed by ElexoPharm and Orphagen Pharmaceuticals, will continue to drive growth in the sales of the steroidogenesis inhibitors after 2018.

Securing Formal Approval of Ketoconazole HRA and Metopirone for Cushing’s Syndrome Will Broaden Their Availability to Patients

Ketoconazole is a popular off-label drug used to treat CS sufferers; however, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have recently restricted patients’ access to the medical therapy owing to its negative risk/benefit ratio. Subsequently, the pharmacological agent is only obtainable from hospital pharmacies. The French pharmaceutical company, HRA Pharma, is on the cusp of obtaining official approval for Ketoconazole HRA (ketoconazole), indicated explicitly for the management of CS patients in Europe. If granted marketing authorization, patients will have greater access to the drug and the company will generate an additional source of revenue. GlobalData believes that ketoconazole will continue to play an integral role in managing CS patients during the forecast period, owing to its respectable efficacy, economical price tag, and the high-costs associated with the newer, pipeline agents entering the market. Furthermore, the Parisian-based drug developer is also conducting a global, prospective Phase III/IV trial evaluating Metopirone’s safety and efficacy in CS sufferers. Metopirone (metyrapone) is a licensed medical therapy used in CS within Europe, but is only indicated for use as a diagnostic tool in the US.

What Do Physicians Think?

The KOLs interviewed by GlobalData for the purposes of this report highlighted an array of fundamental issues surrounding the diagnosis and treatment of CS. Pioneering leaders within the field of CS, who have participated in pivotal clinical trials, delivered expert insights into current treatment paradigms, including unearthing limitations of existing medical therapies and stressing areas of unmet need that necessitate attention.

“Patients with Cushing’s generally have [a] very poor quality of life, both in active disease and when they are cured. When we are finally able to control [the] symptoms, quality of life improves, but never returns back to normal.”

EU Key Opinion Leader

“Many of the symptoms are not specific and it’s not until they all come together, or the patient really feels awful, or someone suddenly thinks of it, [that they are diagnosed]. It can take months, if not several years, to get diagnosed because they can be sent because of obesity, because of hypertension, because of diabetes, which is difficult to control, [or because of] bruising or depression.”

EU Key Opinion Leader
Executive Summary

“There’s been nothing for these patients until the last three or four years, and now there’s a glut of drugs which are useful.”

EU Key Opinion Leader

“There’s a need for a drug that targets the pituitary tumor, itself, without risk. Signifor is the only one that does target the tumor, but the problem is the risk of hyperglycemia. I think that’s where the unmet need is.”

US Key Opinion Leader

“For aggressive Cushing’s, sometimes even using all the drugs we have, we still have problems completely stopping cortisol.”

EU Key Opinion Leader

“[Cushing’s syndrome] is a rare disease. Probably only physicians that know the disease well should take care of [it].”

EU Key Opinion Leader

“[We need] a more reasonable medical approach, for example, what to do first, what to do second, which is the best among all the drugs we have. [We need] a reasonable algorithm that is not based on personal experience.”

EU Key Opinion Leader

“In Cushing’s disease, there are probably other pathways that could be targeted. But, for the moment, it’s only basic research, and I don’t really know when we might have something else on the other pathways. So, for the moment, other than somatostatin receptors, I do not think that there might be anything really promising in terms of basic research.”

EU Key Opinion Leader

“I think [the pipeline] is stronger than in other years. In a year, we’ll really know more about the new drugs. We have short-term data but we need more data, especially for NormoCort, where we probably need a year and a half or two years of studies to see if it’s safe, how it’s doing, and if it actually works.”

US Key Opinion Leader

“I think [NormoCort (COR-003) is] a promising drug because it’s derived from ketoconazole and it’s supposed to be more efficient and less toxic. I think if it stands up to the standards they have been telling us about, [then,] I think it should be a very good alternative that I’m really looking forward to be able to use.”

EU Key Opinion Leader

“[LCI699] is a drug that acts on the adrenal and is an enzyme blocker; it’s also a good possibility…I think it’s an interesting drug to have around.”

EU Key Opinion Leader
# Table of Contents

1 **Table of Contents** ....................................................................................................................... 8

1.1 List of Tables .................................................................................................................... 12

1.2 List of Figures ................................................................................................................... 14

2 **Introduction** ............................................................................................................................... 16

2.1 Catalyst ............................................................................................................................. 16

2.2 Related Reports ................................................................................................................ 17

2.3 Upcoming Related Reports ............................................................................................... 17

3 **Disease Overview** ..................................................................................................................... 18

3.1 Etiology and Pathophysiology ........................................................................................... 19

3.2 Prognosis .......................................................................................................................... 21

3.3 Quality of Life .................................................................................................................... 22

3.4 Symptoms ......................................................................................................................... 23

3.5 Diagnosis .......................................................................................................................... 25

4 **Epidemiology** ............................................................................................................................ 30

4.1 Disease Background ......................................................................................................... 30

4.2 Risk Factors and Comorbidities ....................................................................................... 31

4.3 Global Trends ................................................................................................................... 32

4.3.1 US ................................................................................................................................. 32

4.3.2 EU ................................................................................................................................. 32

4.4 Forecast Methodology ....................................................................................................... 33

4.4.1 Sources Used ................................................................................................................ 36

4.4.2 Sources Not Used ......................................................................................................... 38

4.4.3 Forecast Assumptions and Methods – Prevalent Cases ............................................... 39

4.4.4 Forecast Assumptions and Methods – Immediate TSS Outcomes ............................... 40

4.5 Epidemiological Forecast for Cushing’s Syndrome (2013–2023) ...................................... 40

4.5.1 Cushing’s Syndrome ..................................................................................................... 40
Table of Contents

4.5.2 Cushing’s Disease ..........................................................46
4.5.3 Ectopic Adrenocorticotropic Hormone Cushing’s Syndrome ..................................51
4.5.4 Adrenal Adenoma Cushing’s Syndrome .........................................................57
4.5.5 Adrenal Carcinoma Cushing’s Syndrome .........................................................62
4.5.6 Age-Standardized Diagnosed Prevalence Rates ..............................................67
4.5.7 Immediate Transsphenoidal Adenomectomy Surgery Outcomes ....................69
4.6 Discussion ....................................................................................70
   4.6.1 Epidemiological Forecast Insight ...............................................................70
   4.6.2 Limitations of the Analysis .........................................................................71
   4.6.3 Strengths of the Analysis ............................................................................71
5 Current Treatment Options ............................................................................73
   5.1 Overview .................................................................................................73
   5.2 Treatment Approach ...................................................................................74
   5.3 Product Profiles – Major Brands .................................................................78
      5.3.1 Signifor (pasireotide) and Signifor LAR (pasireotide) ...............................78
      5.3.2 Korlym (mifepristone) ............................................................................87
      5.3.3 Ketoconazole and Ketoconazole HRA (ketoconazole) ............................96
      5.3.4 Metopirone (metyrapone) .....................................................................103
      5.3.5 Lysodren (mitotane) ...............................................................................109
6 Unmet Needs Assessment and Opportunity Analysis .........................................114
   6.1 Overview ....................................................................................................114
   6.2 Unmet Needs Analysis ................................................................................115
      6.2.1 Unmet Need: Effective Drugs Directed against the Underlying Cause of Cushing’s Disease .................................................................115
      6.2.2 Unmet Need: Few Drugs – Especially Those for Severe Cushing’s Syndrome – Possess Favorable Safety and Efficacy .........................................................116
      6.2.3 Unmet Need: Physician Awareness of Cushing’s Syndrome Symptomatology ..........118
## Table of Contents

6.2.4 Unmet Need: Accelerated Referral Systems to Specialists in Secondary and Tertiary Care Settings ................................................................. 119

6.2.5 Unmet Need: Uniform Guidelines Unambiguously Defining Treatment and Remission 121

6.3 Opportunity Analysis ........................................................................................................... 121

6.3.1 Opportunity: Development of Improved Adrenocorticotropic Hormone Modulator Drugs ................................................................................................................................... 121

6.3.2 Opportunity: Reformulation of the Steroidogenic Inhibitors into Longer-Acting Release Treatments ................................................................................................................. 122

6.3.3 Opportunity: Development of Universally Accepted Tests and Measures for Better Diagnosis and Monitoring of Cushing’s Syndrome Activity and Treatment Response 122

6.3.4 Opportunity: Prospective, Randomized Trials for Off-Label Cushing’s Syndrome Agents ................................................................................................................................... 123

6.3.5 Opportunity: Gaining Understanding of the Pathophysiology of Cushing’s Syndrome 124

7 Research and Development Strategies ................................................................................ 125

7.1 Overview ......................................................................................................................... 125

7.1.1 Inhibitors of Cortisol Synthesis in the Adrenal Glands ................................................. 125

7.1.2 Licensing Agreements, Partnerships, and Alliances .................................................... 126

7.1.3 Secondary Indications ................................................................................................. 127

7.2 Clinical Trial Design ........................................................................................................ 128

7.2.1 Selecting Suitable Comparator Arms ........................................................................... 128

7.2.2 Evaluating and Determining Appropriate Clinical Trial Endpoints ............................ 129

7.2.3 Accurately Representing the Patient Population in Clinical Trials ............................ 131

8 Pipeline Assessment ........................................................................................................... 135

8.1 Overview ......................................................................................................................... 135

8.2 Promising Drugs in Clinical Development ........................................................................ 135

8.2.1 NormoCort (COR-003) ............................................................................................ 136

8.2.2 LCI699 ...................................................................................................................... 141

8.3 Innovative Early-Stage Approaches ................................................................................. 146

8.3.1 Somatoprim (DG3173) ............................................................................................. 147
# Table of Contents

8.3.2 Anti-Sense Technology and RNA Interference ............................................................ 147  
8.3.3 Retinoic Acid ............................................................................................................... 148  
8.3.4 Other Early-Stage Approaches and Non-Pharmacotherapies...................................... 149  

9 Pipeline Valuation Analysis .............................................................................................. 151  
9.1 Clinical Benchmark of Key Pipeline Drugs ................................................................. 151  
9.2 Commercial Benchmark of Key Pipeline Drugs .......................................................... 153  
9.3 Competitive Assessment ............................................................................................... 154  
9.4 Top-Line Five-Year Forecast .......................................................................................... 156  
9.4.1 US............................................................................................................................... 158  
9.4.2 5EU............................................................................................................................. 159  

10 Appendix................................................................................................................................. 161  
10.1 Bibliography .................................................................................................................... 161  
10.2 Abbreviations .................................................................................................................. 178  
10.3 Methodology ................................................................................................................... 180  
10.4 Forecasting Methodology ............................................................................................... 180  
10.4.1 Diagnosed Cushing’s Syndrome Patients ............................................................ 180  
10.4.2 Percent Drug-Treated Patients ................................................................................ 181  
10.4.3 Drugs Included in Each Therapeutic Class ........................................................... 181  
10.4.4 Launch and Patent Expiry Dates ................................................................................. 182  
10.4.5 General Pricing Assumptions .................................................................................... 183  
10.4.6 Individual Drug Assumptions .................................................................................... 183  
10.4.7 Pricing of Pipeline agents ......................................................................................... 187  
10.5 Physicians and Specialists Included in This Study ......................................................... 189  
10.6 About the Authors ........................................................................................................... 190  
10.6.1 Analyst ....................................................................................................................... 190  
10.6.2 Therapy Director ....................................................................................................... 190  
10.6.3 Epidemiologist ......................................................................................................... 191
Table of Contents

10.6.4 Global Head of Healthcare ........................................................................................................... 192
10.7 About GlobalData ............................................................................................................................. 193
10.8 Disclaimer ........................................................................................................................................ 193

1.1 List of Tables
Table 1: Various Subtypes of Endogenous Cushing’s Syndrome .......................................................... 19
Table 2: Symptoms of Cushing’s Syndrome ............................................................................................... 25
Table 3: Risk Factors for Cushing’s Syndrome .......................................................................................... 32
Table 4: 6MM, Sources of CS Prevalence Data .......................................................................................... 34
Table 5: 6MM, Diagnosed Prevalent Cases of CS, Ages ≥18 Years, Both Sexes, N, Selected Years 2013– 2023 .............................................................................................................................................. 41
Table 6: 6MM, Age-Specific Diagnosed Prevalent Cases of CS, Both Sexes, N (Row %), 2013 .......... 43
Table 7: 6MM, Sex-Specific Diagnosed Prevalent Cases of CS, Ages ≥18 Years, N (Row %), 2013 ....... 45
Table 8: 6MM, Diagnosed Prevalent Cases of Cushing’s Disease, Ages ≥18 Years, Both Sexes, N, Selected Years 2013–2023 ...................................................................................................................... 47
Table 9: 6MM, Age-Specific Diagnosed Prevalent Cases of Cushing’s Disease, Both Sexes, N (Row %), 2013 ....................................................................................................................................................... 48
Table 10: 6MM, Sex-Specific Diagnosed Prevalent Cases of Cushing’s Disease, Ages ≥18 Years, N (Row %), 2013 ............................................................................................................................................... 50
Table 11: 6MM, Diagnosed Prevalent Cases of Ectopic ACTH CS, Ages ≥18 Years, Both Sexes, N, Selected Years 2013–2023 ...................................................................................................................... 52
Table 12: 6MM, Age-Specific Diagnosed Prevalent Cases of Ectopic ACTH CS, Both Sexes, N (Row %), 2013 .......................................................................................................................................................... 54
Table 13: 6MM, Sex-Specific Diagnosed Prevalent Cases of Ectopic ACTH CS, Ages ≥18 Years, N (Row %), 2013 .......................................................................................................................................................... 56
Table 14: 6MM, Diagnosed Prevalent Cases of Adrenal Adenoma CS, Ages ≥18 Years, Both Sexes, N, Selected Years 2013–2023 ...................................................................................................................... 58
Table of Contents

Table 15: 6MM, Age-Specific Diagnosed Prevalent Cases of Adrenal Adenoma CS, Both Sexes, N (Row %), 2013 ................................................................. 59

Table 16: 6MM, Sex-Specific Diagnosed Prevalent Cases of Adrenal Adenoma CS, Ages ≥18 Years, N (Row %), 2013 .................................................................................. 61

Table 17: 6MM, Diagnosed Prevalent Cases of Adrenal Carcinoma CS, Ages ≥18 Years, Both Sexes, N, Selected Years 2013–2023 .................................................................................. 63

Table 18: 6MM, Age-Specific Diagnosed Prevalent Cases of Adrenal Carcinoma CS, Both Sexes, N (Row %), 2013 .................................................................................. 64

Table 19: 6MM, Sex-Specific Diagnosed Prevalent Cases of Adrenal Carcinoma CS, Ages ≥18 Years, N (Row %), 2013 ........................................................................................ 66

Table 20: 6MM, Immediate TSS Outcomes, Both Sexes, N, 2013 .................................................................................. 70

Table 21: Leading Pharmacological Treatments for Cushing’s Syndrome .................................................................................. 77

Table 22: Product Profile – Signifor .................................................................................. 82

Table 23: Signifor SWOT Analysis .................................................................................. 86

Table 24: Product Profile – Korlym .................................................................................. 91

Table 25: Korlym SWOT Analysis .................................................................................. 95

Table 26: Product Profile – Nizoral .................................................................................. 100

Table 27: Ketoconazole SWOT Analysis .......................................................................... 102

Table 28: Product Profile – Metopirone .......................................................................... 106

Table 29: Metopirone SWOT Analysis .......................................................................... 108

Table 30: Product Profile – Lysodren ............................................................................. 111

Table 31: Lysodren SWOT Analysis ............................................................................. 113

Table 32: Overall Unmet Needs – Current Level of Attainment ....................................... 114

Table 33: Clinical Trial Design of Key Marketed and Pipeline Drugs for Cushing’s Syndrome, August 2014 ............................................................................. 133

Table 34: Cushing’s Syndrome – Late Stage Pipeline, 2014 .............................................. 135
Table of Contents

Table 35: Product Profile – NormoCort (COR-003) ................................ ................................ .................... 138
Table 36: NormoCort (COR-003) SWOT Analysis .............................................................................. 140
Table 37: Product Profile – LCI699 .................................................................................................. 143
Table 38: LCI699 SWOT Analysis .................................................................................................... 145
Table 39: Early-Stage Pipeline Products in Cushing’s Syndrome .................................................... 146
Table 40: Clinical Benchmark of Key Pipeline Drugs ...................................................................... 152
Table 41: Commercial Benchmark of Key Pipeline Drugs ................................................................. 153
Table 42: Top-Line Sales Forecasts ($) for Cushing’s Syndrome, 2013–2018 ...................................... 157
Table 43: Key Events Impacting Sales for Cushing’s Syndrome, 2013–2018 ..................................... 157
Table 44: Cushing’s Syndrome – Drivers and Barriers, 2013–2018 .................................................. 160
Table 45: Abbreviations ..................................................................................................................... 178
Table 46: Key Launch Dates .............................................................................................................. 182
Table 47: Key Patent Expiries ............................................................................................................ 182

1.2 List of Figures

Figure 1: Pathophysiology of Cushing’s Syndrome ........................................................................... 21
Figure 2: The Diagnosis Algorithm for Cushing’s Syndrome ............................................................. 28
Figure 3: The Diagnosis Algorithm for ACTH-Dependent Cushing’s Syndrome .............................. 29
Figure 4: 6MM, Diagnosed Prevalent Cases of CS, Ages ≥18 Years, Both Sexes, N, 2013–2023 .......... 42
Figure 5: 6MM, Age-Specific Diagnosed Prevalent Cases of CS, Both Sexes, N, 2013 ................... 44
Figure 6: 6MM, Sex-Specific Diagnosed Prevalent Cases of CS, Ages ≥18 Years, N, 2013 ............. 46
Figure 7: 6MM, Diagnosed Prevalent Cases of Cushing’s Disease, Ages ≥18 Years, Both Sexes, N, 2013–2023 ....................................................................................................................... 47
Figure 8: 6MM, Age-Specific Diagnosed Prevalent Cases of Cushing’s Disease, Both Sexes, N, 2013 ...... 49
Figure 9: 6MM, Sex-Specific Diagnosed Prevalent Cases of Cushing's Disease, Ages ≥18 Years, N, 2013 51

Figure 10: 6MM, Diagnosed Prevalent Cases of Ectopic ACTH CS, Ages ≥18 Years, Both Sexes, N, 2013–2023.................................................................53

Figure 11: 6MM, Age-Specific Diagnosed Prevalent Cases of Ectopic ACTH CS, Both Sexes, N, 2013....55

Figure 12: 6MM, Sex-Specific Diagnosed Prevalent Cases of Ectopic ACTH CS, Ages ≥18 Years, N, 2013.57

Figure 13: 6MM, Diagnosed Prevalent Cases of Adrenal Adenoma CS, Ages ≥18 Years, Both Sexes, N, 2013–2023.................................................................58

Figure 14: 6MM, Age-Specific Diagnosed Prevalent Cases of Adrenal Adenoma CS, Both Sexes, N, 2013..60

Figure 15: 6MM, Sex-Specific Diagnosed Prevalent Cases of Adrenal Adenoma CS, Ages ≥18 Years, N, 2013.................................................................62

Figure 16: 6MM, Diagnosed Prevalent Cases of Adrenal Carcinoma CS, Ages ≥18 Years, Both Sexes, N, 2013–2023.................................................................63

Figure 17: 6MM, Age-Specific Diagnosed Prevalent Cases of Adrenal Carcinoma CS, Both Sexes, N, 2013 .............................................................................65

Figure 18: 6MM, Sex-Specific Diagnosed Prevalent Cases of Adrenal Carcinoma CS, Ages ≥18 Years, N, 2013.................................................................67

Figure 19: 6MM, Age-Standardized Diagnosed Prevalence of CS (%), Ages ≥18 Years, 2013........68

Figure 20: 6MM, Age-Standardized Diagnosed Prevalence of Cushing's Disease (%), Ages ≥18 Years, 2013 .................................................................69

Figure 21: Treatment Paradigm for Cushing's Syndrome .................................................................76

Figure 22: Competitive Assessment of Late-Stage Pipeline Agents in Cushing's Syndrome, 2013–2018 ....156
Introduction

2  Introduction

2.1  Catalyst

The global Cushing’s syndrome (CS) market has undergone considerable transition in recent years. Prior to the introduction of Korlym (mifepristone) and Signifor (pasireotide) to the market, the CS landscape was barren and the pipeline sterile; physicians were compelled to prescribe off-label medications, such as ketoconazole, cabergoline, bromocriptine, and etomidate, in order to effectively normalize patients’ elevated cortisol levels. However, these pharmacotherapies have disturbing side effect profiles and, with time, some of them become ineffective. The arrival of Korlym and Signifor equipped physicians with clinically-evaluated products, specifically licensed for CS. Nonetheless, these medical treatments still present troublesome adverse effects and/or unconvincing efficacies, thus discouraging healthcare professionals from readily adopting them into their treatment protocols as first-line agents. Between 2013 and 2018, GlobalData expects the CS market to experience further significant growth; as additional novel agents progress through pivotal, late-stage trials, the number of diagnosed prevalence cases of CS across the US and the five European Union countries (5EU) (France, Germany, Italy, Spain, and UK) will increase, and patient access to existing pharmacological therapies will expand.

The need for alternative medical options that demonstrate superior safety and efficacy has been recognized, and Novartis and Cortendo AB have responded with the development of LCI699 and NormoCort (COR-003), respectively. These novel steroidogenesis inhibitors will advance treatment patterns for CS patients, offering hope to a myriad of sufferers. Oral generic ketoconazole’s usage and availability has been restricted with the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) warning that, when used for its intended indication for fungal infections, the risk of hepatotoxicity now outweighs the drug’s benefits. Consequently, CS patients can now only obtain oral ketoconazole from tightly regulated environments, such as hospital pharmacies. HRA Pharma’s Ketoconazole HRA (ketoconazole) was awarded a positive opinion by the Committee for Medicinal Products for Human Use (CHMP) and was recommended for approval to the European Commission. GlobalData anticipates that HRA Pharma will launch Ketoconazole HRA in Europe in 2015, broadening the medicine’s availability. This combination of key events occurring during the five-year forecast period will contribute to the evolution of the CS marketplace and has inspired GlobalData to publish a report on this particular indication, as it is set to enter a new exciting phase.
Introduction

2.2 Related Reports


2.3 Upcoming Related Reports

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, San Francisco, Boston, London, India, Korea, Japan, Singapore, and Australia.

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