Multiple Sclerosis Therapeutics to 2019

Treatment Diversification, Increasing Efficacy, and Pipeline Innovation Combine to Drive Growth
GBI Research Report Guidance

- Chapter two gives an overview of Multiple Sclerosis (MS) epidemiology, pathogenesis, diagnosis, and as well as the therapeutic unmet need therapeutically of the indication.

- Chapter three gives an overview of the currently available treatments for multiple sclerosis MS including all first, second and third-line therapies as well as an outline of their revenues, efficacy, safety, and future prospects.

- Chapter four provides in-depth analysis of the pipeline drug analysis of the MS therapeutic pipeline and subsequent to this an overview of seven promising pipeline molecules in later-stage trials that look set to make a significant impact on the market.

- Chapter five forecasts the revenue of the major global gives predicted market forecasts for the major global pharmaceutical markets of the US, UK, France, Spain, Italy and Japan until 2019 in relation to MS.

- Chapter six provides an overview of notable co-development and licensing deals in the MS market.
Executive Summary

Sustained Growth of the Multiple Sclerosis Market

The Multiple Sclerosis (MS) market has been growing consistently over the last two decades and is forecast to continue to grow from $XX billion in 2012 to $XX billion by 2019 at a CAGR of XX%. The US will remain the biggest market, constituting approximately XX% of the total by 2019, although this represents little change in the intervening years. Despite some countries in the EU growing more slowly in terms of prevalence than others (such as Germany and Spain), the European market in general will grow due to population growth and subsequent patient-population growth, higher drug prices, and strong uptake due to more expensive and efficacious pipeline drugs. Japan will remain of little significance owing to the very low prevalence population and continued negligible percentage of the overall market, despite high drug prices.

The Multiple Sclerosis Therapeutic Landscape is in a State of Transition

The therapeutic landscape for MS is undergoing profound change in terms of drug types, drug targets, drug safety, and above all, drug efficacy. The current treatment options, namely Copaxone (glatiramer acetate), Avonex (interferon beta 1a IM), Rebif (interferon beta 1a SC) and Betaseron (interferon beta 1b), are beginning to be supplanted by both recently approved and, within the forecast period, late-stage pipeline molecules, such as Gilenya (fingolimod hydrochloride), Tecfidera (dimethyl fumarate), Lemtrada (alemtuzumab) and Aubagio (teriflunomide), which offer better overall efficacy and safety profiles. Additionally, a high proportion of newly approved drugs are oral therapies, rather than the previously used injectable therapies. They offer greater convenience, which, coupled with the increased efficacy, is expected to result in a new standard of treatment as older drugs are gradually replaced with first-line options in the treatment algorithm. This is already happening as new oral drug Tecfidera begins to establish itself in the market. The pipeline also offers more in terms of second-line therapies, as a swathe of effective monoclonal Antibody (mAb) therapies make their way through clinical trials. This will further contribute to the reshuffle, offering patients a more diverse and, more importantly, safer selection of second-line therapies that had, until now, been dominated by Tysabri.
# Table of Contents

1. **Table of Contents** .................................................................................................................. 5
   1.1 List of Tables .......................................................................................................................... 7
   1.2 List of Figures ....................................................................................................................... 8

2. **Introduction** ......................................................................................................................... 9
   2.1 Disease Overview ................................................................................................................. 9
   2.2 Epidemiology .......................................................................................................................... 9
   2.3 Symptoms ............................................................................................................................... 10
   2.4 Etiology .................................................................................................................................. 10
   2.5 Pathophysiology .................................................................................................................... 11
     2.5.1 Blood Brain Barrier Degradation ................................................................................. 11
     2.5.2 Cellular Infiltration of the Central Nervous System ................................................... 11
   2.6 Co-morbidities/Complications .............................................................................................. 12
   2.7 Diagnosis ............................................................................................................................... 13
     2.7.1 McDonald Criteria ........................................................................................................... 13
     2.7.2 Physical Examination ...................................................................................................... 14
     2.7.3 MRI Scans ........................................................................................................................ 14
     2.7.4 Lumbar Puncture ............................................................................................................. 14
     2.7.5 Other Diagnostic Tests .................................................................................................. 14
   2.8 Prognosis ................................................................................................................................ 15
   2.9 Treatment Efficacy .............................................................................................................. 16
   2.10 Treatment Options .............................................................................................................. 16
     2.10.1 Corticosteroids ............................................................................................................... 17
     2.10.2 Anti-neoplastic Drugs .................................................................................................... 17
     2.10.3 Skeletal Muscle Relaxants ............................................................................................. 17
     2.10.4 Pain Management in MS ............................................................................................... 18
   2.11 Treatment Algorithm ........................................................................................................... 18
   2.12 Non-pharmacological Therapies ......................................................................................... 20

3. **Therapeutic Landscape** ....................................................................................................... 21
   3.1 Copaxone (glatiramer acetate) – Teva Pharmaceuticals ....................................................... 21
   3.2 Betaseron (interferon beta 1b) – Bayer AG ........................................................................... 22
   3.3 Avonex (interferon beta 1a IM) – Biogen ................................................................................ 23
   3.4 Rebif (interferon beta 1a SC) – Merck Serono ....................................................................... 24
   3.5 Tysabri (natalizumab) – Biogen Idec/Elan Corporation ......................................................... 25
   3.6 Gilenya (fingolimod hydrochloride) – Mitsubishi Tanabe and Novartis ......................... 26
   3.7 Aubagio (Teriflunomide) – Genzyme Corporation and Sanofi-Aventis ......................... 27
   3.8 Novantrone (mitoxantrone ) – Merck Serono ................................................................. 27
   3.9 Conclusion .............................................................................................................................. 29
   3.10 Unmet Need ........................................................................................................................ 29

4. **Pipeline for Multiple Sclerosis Therapeutics** ..................................................................... 30
   4.1 Overall Pipeline .................................................................................................................... 30
   4.2 Route of Administration ....................................................................................................... 32
   4.3 Molecular Targets within the MS Pipeline .......................................................................... 33
   4.4 Clinical Trials ....................................................................................................................... 35
     4.4.1 Failure Rate of Developmental Programs ................................................................... 35
     4.4.2 Clinical Trial Size ......................................................................................................... 37
     4.4.3 Clinical Trial Duration ................................................................................................. 39
   4.5 Promising Pipeline Candidates ......................................................................................... 41
     4.5.1 Lemtrada (alemtuzumab) – Genzyme and Bayer Schering Pharma ......................... 41
     4.5.2 Tecfidera (dimethyl fumarate) – Biogen Idec ............................................................ 41
     4.5.3 Laquinimod (laquinimod sodium) – Teva Pharmaceuticals ....................................... 42
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5.4 ocrelizumab – F. Hoffman-La Roche</td>
<td>43</td>
</tr>
<tr>
<td>4.5.5 daclizumab – Biogen Idec and Abbot Laboratories</td>
<td>43</td>
</tr>
<tr>
<td>4.5.6 filgrastim – GlaxoSmithKline</td>
<td>44</td>
</tr>
<tr>
<td>4.5.7 Siponimod (BAF-312) – Novartis AG</td>
<td>45</td>
</tr>
<tr>
<td>4.6 Conclusion</td>
<td>45</td>
</tr>
<tr>
<td>5 Market Forecast to 2019</td>
<td>48</td>
</tr>
<tr>
<td>5.1 Geographical Markets</td>
<td>48</td>
</tr>
<tr>
<td>5.1.1 Key Developed Markets</td>
<td>48</td>
</tr>
<tr>
<td>5.1.2 US</td>
<td>51</td>
</tr>
<tr>
<td>5.1.3 Top Five EU Countries</td>
<td>53</td>
</tr>
<tr>
<td>5.1.4 Japan</td>
<td>57</td>
</tr>
<tr>
<td>5.2 Drivers and Barriers</td>
<td>59</td>
</tr>
<tr>
<td>5.2.1 Drivers</td>
<td>59</td>
</tr>
<tr>
<td>5.2.2 Barriers</td>
<td>60</td>
</tr>
<tr>
<td>6 Deals and Strategic Consolidations</td>
<td>62</td>
</tr>
<tr>
<td>6.1 Major Co-development Deals</td>
<td>62</td>
</tr>
<tr>
<td>6.1.1 Daiichi Sankyo Enters into an Agreement with Amplimmune</td>
<td>64</td>
</tr>
<tr>
<td>6.1.2 Karo Bio Enters into an Agreement with Pfizer</td>
<td>64</td>
</tr>
<tr>
<td>6.1.3 Proteostasis Enters into an Agreement with Elan</td>
<td>64</td>
</tr>
<tr>
<td>6.1.4 Lycera Enters into an Agreement with Merck</td>
<td>65</td>
</tr>
<tr>
<td>6.1.5 Facet Enters into an Agreement with Trubion</td>
<td>65</td>
</tr>
<tr>
<td>6.1.6 UCB Enters into an Agreement with Biogen</td>
<td>65</td>
</tr>
<tr>
<td>6.2 Major Licensing Deals</td>
<td>66</td>
</tr>
<tr>
<td>6.2.1 Addex Extends its Licensing Agreement with Merck</td>
<td>69</td>
</tr>
<tr>
<td>6.2.2 Biogen Enters into a Licensing Agreement with Acorda Therapeutics</td>
<td>70</td>
</tr>
<tr>
<td>6.2.3 Genzyme Enters into a Licensing Agreement with Bayer Healthcare</td>
<td>70</td>
</tr>
<tr>
<td>6.2.4 Novartis Enters into a Licensing Agreement with Peptimmune</td>
<td>70</td>
</tr>
<tr>
<td>6.2.5 Merck Serono Enters into a Licensing Agreement with Apitope Technology</td>
<td>70</td>
</tr>
<tr>
<td>6.2.6 Antisense Enters into a Licensing Agreement with Teva Pharmaceutical</td>
<td>71</td>
</tr>
<tr>
<td>6.2.7 BioMS Medical Corp Enters into a Licensing Agreement with Eli Lilly</td>
<td>71</td>
</tr>
<tr>
<td>6.2.8 Biotica Enters into an Agreement with Wyeth</td>
<td>71</td>
</tr>
<tr>
<td>7 Appendix</td>
<td>72</td>
</tr>
<tr>
<td>7.1 Pipeline Product Tables by Phase</td>
<td>72</td>
</tr>
<tr>
<td>7.2 Market Forecasting Data Tables to 2019</td>
<td>82</td>
</tr>
<tr>
<td>7.3 Market Definition</td>
<td>86</td>
</tr>
<tr>
<td>7.4 Abbreviations</td>
<td>86</td>
</tr>
<tr>
<td>7.5 References</td>
<td>87</td>
</tr>
<tr>
<td>7.6 Methodology</td>
<td>90</td>
</tr>
<tr>
<td>7.7 Secondary Research</td>
<td>91</td>
</tr>
<tr>
<td>7.8 Therapeutic Landscape</td>
<td>91</td>
</tr>
<tr>
<td>7.9 Epidemiology-Based Forecasting</td>
<td>92</td>
</tr>
<tr>
<td>7.10 Market Size by Geography</td>
<td>93</td>
</tr>
<tr>
<td>7.11 Pipeline Analysis</td>
<td>94</td>
</tr>
<tr>
<td>7.12 Contact Us</td>
<td>94</td>
</tr>
<tr>
<td>7.13 Disclaimer</td>
<td>94</td>
</tr>
</tbody>
</table>
1.1 List of Tables

Table 1: McDonald Criteria, Multiple Sclerosis, 2013 ................................................................. 13
Table 2: Expanded Disability Status Scale, Multiple Sclerosis, 2013 ........................................ 15
Table 3: Multiple Sclerosis, Global, Market Forecast, ($bn), 2012–2019 ................................. 82
Table 4: Multiple Sclerosis, US, Market Forecast, ($bn), 2012–2019 ....................................... 82
Table 5: Multiple Sclerosis, UK, Market Forecast, ($bn), 2012–2019 ...................................... 83
Table 6: Multiple Sclerosis, France, Market Forecast, ($bn), 2012–2019 ............................... 83
Table 7: Multiple Sclerosis, Germany, Market Forecast, ($bn), 2012–2019 ......................... 84
Table 8: Multiple Sclerosis, Italy, Market Forecast, ($bn), 2012–2019 ..................................... 84
Table 9: Multiple Sclerosis, Spain, Market Forecast, ($bn), 2012–2019 ................................. 85
Table 10: Multiple Sclerosis, Japan, Market Forecast, ($bn), 2012–2019 ............................... 85
1.2 List of Figures

Figure 1: Treatment Algorithm, Global, Multiple Sclerosis, 2013 ............................................................ 19
Figure 2: Multiple Sclerosis, Marketed Products Heat Map ................................................................. 28
Figure 3: Overall Pipeline for Multiple Sclerosis ..................................................................................... 31
Figure 4: Routes of Administration in the Pipeline .................................................................................. 32
Figure 5: Molecular Targets of Pipeline Molecules .................................................................................. 33
Figure 6: Molecular Targets in MS Pipeline by Phase of Development ................................................ 34
Figure 7: Failure Rate of MS Clinical Trials, 2006–2013 ..................................................................... 36
Figure 8: Reasons for Clinical Trial Failure, 2006–2013 ................................................................. 37
Figure 9: Clinical Trial Size by Product and Phase, 2006–2013 ............................................................ 38
Figure 10: Clinical Trial Duration by Phase and Molecule Type, 2006–2013 ..................................... 40
Figure 11: Multiple Sclerosis, Pipeline Product Heat Map ............................................................... 46
Figure 12: Multiple Sclerosis, Marketed Product Heat Map, 2012–2019 ............................................. 47
Figure 13: Multiple Sclerosis Market, Global, Patient Volumes (’000) and Market Size ($bn), 2012–2019 ......... 50
Figure 14: Multiple Sclerosis Market, US, Patient Volumes (’000), Annual Cost of Treatment ($) and Market Size ($bn), 2012–2019 ................................................................. 52
Figure 15: Multiple Sclerosis Market, EU5, Patient Population (’000), 2012–2019 ............................... 54
Figure 16: Multiple Sclerosis Market, EU5, Annual Cost of Treatment ($), 2012–2019 ....................... 55
Figure 17: Multiple Sclerosis Market, EU5, Market Size ($bn), 2013–2019 ............................................. 56
Figure 18: Multiple Sclerosis Market, Japan, Patient Volume (’000), Annual Cost of Treatment ($) and Market Size ($bn), 2013–2019 ................................................................. 58
Figure 19: Multiple Sclerosis, Co-development Deals by Geography, Value and Year, 2006–2013 ............. 62
Figure 20: Multiple Sclerosis, Co-Development Deal Frequency by Phase and Molecule Type 2006–2013 .. 63
Figure 21: Multiple Sclerosis, Licensing Deals by Geography, Value and Year, 2006–2013 ................... 67
Figure 22: Multiple Sclerosis, Licensing Deal frequency by Phase and Molecule Type, 2006–2013 .......... 68
Figure 23: Multiple Sclerosis, Licensing Deal Value by Molecule Type and Mechanism of Action, 2006–2013 ...... 69
Figure 24: Multiple Sclerosis, Global, Pharmaceutical Pipeline (Discovery) ........................................... 72
Figure 25: Multiple Sclerosis, Global, Pharmaceutical Pipeline (Pre-Clinical)-I ....................................... 73
Figure 26: Multiple Sclerosis, Global, Pharmaceutical Pipeline (Pre-Clinical)-II ..................................... 74
Figure 27: Multiple Sclerosis, Global, Pharmaceutical Pipeline (Pre-Clinical)-III ................................. 75
Figure 28: Multiple Sclerosis, Global, Pharmaceutical Pipeline (Phase I) -I ........................................... 76
Figure 29: Multiple Sclerosis, Global, Pharmaceutical Pipeline (Phase I) -II ........................................... 77
Figure 30: Multiple Sclerosis, Global, Pharmaceutical Pipeline (Phase II) - I ......................................... 78
Figure 31: Multiple Sclerosis, Global, Pharmaceutical Pipeline (Phase II) - II ......................................... 79
Figure 32: Multiple Sclerosis, Global, Pharmaceutical Pipeline (Phase III) ............................................ 80
Figure 33: Multiple Sclerosis, Global, Pharmaceutical Pipeline (Pre-Registration) ............................. 80
Figure 34: Multiple Sclerosis, Global, Pharmaceutical Pipeline (Undisclosed) ...................................... 81
Figure 35: Multiple Sclerosis Market, Global, GBI Research Market Sizing Model ............................ 93
2 Introduction

2.1 Disease Overview

MS is an inflammatory disease characterized by the autoimmune attack on the insulating myelin sheath around neuron axons in both the central and peripheral nervous systems. The progressive degradation of the myelin sheath leads to a growing deterioration of neuronal function often resulting in complete inability to move, eat, or speak. Should the disease run its full course or remain untreated the patient will require full-time care. It can affect anyone and age of onset is usually between XX and XX, with the median being between XX and XX. The disease can be broadly categorized into four subtypes:

- Relapsing Remitting Multiple Sclerosis (RRMS): This is the most common form of MS accounting for approximately XX% of cases. It is characterized by periods of intense disease symptoms (relapses) followed by a remissive period with few or no symptoms. During the remissive states however, continual autoimmune destruction of myelin still occurs and is visible via Magnetic Resonance Imaging (MRI). This is the easiest of the four types to treat and is the main focus of the report.

- Primary Progressive Multiple Sclerosis (PPMS): This type of MS accounts for XX–XX% of all cases. It is characterized by an absence of relapses in the majority of cases and instead a progressive decline in a patient’s ability to function, with symptoms becoming worse as time progresses. This form of the disease is very difficult to treat and as such there are only a small number of drugs approved for it.

- Secondary Progressive Multiple Sclerosis (SPMS): Around half of all cases of RRMS eventually reach a stage where remissive states are less frequent. This is known as SPMS and has much the same outlook as PPMS. The disease becomes steadily worse to the point where it is virtually untreatable. Approximately half of all RRMS sufferers will develop PPMS XX years subsequent to diagnosis and XX% will develop it after XX years (MS Society of Canada, 2013).

- Progressive Relapsing Multiple Sclerosis (PRMS): This is the rarest and most serious form of MS, characterized by a progressive increase in disability coupled with severe, debilitating relapses. There are no periods of remission. It is almost impossible to treat and accounts for around XX% of MS cases.

For many decades the main course of treatment was Intravenous (IV) steroids such as methylprednisolone, as is the standard for nearly every autoimmune disease. However, the last two decades have seen the entry of Disease-Modifying Therapies (DMTs) which not only treat the symptoms, but actually slow disease progression. The classic DMT is interferon beta, which has been approved for MS for nearly two decades and has a well-established safety and efficacy profile. However, in the last decade or so, newer and more effective treatments have gradually begun to emerge in the DMT class and newer standards of treatment are being sought. New oral therapies in particular are starting to emerge and in the future will no doubt be the new standard of MS treatment, coupling ease of administration with robust efficacy and safety.

2.2 Epidemiology

Approximately XX million people worldwide suffer from MS, with around XX in the US alone (Fox, 2010). Areas of high prevalence include most of the seven major developed markets, such as the UK, Germany, France and Italy. The UK and Germany in particular have very high prevalence, with XX and XX sufferers per XX. Like most autoimmune diseases, it affects women more than men, with a ratio of female-to-male sufferers of approximately XX:XX. Diagnosis usually occurs between the ages of XX and XX with a median of XX for women and XX for men. However, pediatric MS is increasingly becoming more prevalent with around XX–XX% of cases being diagnosed before a patient’s 16th birthday. MS is also more common in Caucasians than in other ethnic groups.

MS shows a classic geographical distribution, with certain parts of the world having a much lower prevalence than others. According to the World Health Organization, incidence seems to vary with latitude, increasing in line with distance from the equator. Migrant studies have shown that people emigrating from high-risk areas to low-risk areas are at higher risk of MS than the native population, but surprisingly lower than their country of origin (WHO, 2003).
4.2 Route of Administration

The pipeline for MS is still populated in the majority by small-molecule therapies but biologics have also managed to establish a confident foothold. Small-molecule dominance can be explained by the need for a reliable, safe and efficacious oral drug for the treatment of MS. This aim suits small-molecule drugs more than it does for biologics due to the versatility with which they can be administered.

Of the XX oral therapies in the pipeline with a known molecule type, XX are small molecules and the remaining XX are biologics. This means that in the current MS pipeline, small molecules account for XX% of all oral therapies. The remaining XX small molecules are predominantly injection-based compounds, with a small number being delivered via other means. It should be noted that ‘Other’ denotes less common routes of administration such as inhalation, topical, buccal or nasal. This positioning towards the oral route definitely represents a market transition. (Figure 4, B).

As for the biologics, the predominant route of administration is injection-based. This group incorporates intrathecal, intramuscular, intravenous infusion, injection. Only seven biologics, constituting XX% of the total known, are administered orally, and none are monoclonal antibodies. This is not surprising due to the nature of biologics, namely that if they enter the digestive system they will be broken down by enzymes, resulting in very little of the drug making it to its site of action. However, due to the need in the MS pipeline for a reliable oral therapy, having a drug with that route of administration confers an advantage. This is not to say, however, that there are not still promising biologic pipeline candidates. (Figure 4, C).

Of the known gene therapies, such as stem-cell therapies, all are delivered via an injection-based route. However, gene therapies as a drug candidate are still very much in their infancy. It is entirely possible that in the future, they could become much stronger candidates for a reliable MS treatment.

It should be noted that while there are a number of oral therapies currently approved for MS, these therapies are predominantly general anti-inflammatories such as prednisone. Only Aubagio, Gilenya and the recently approved Tecfidera are not part of this group, but both are hampered by poor safety profiles. As such, the market for oral MS drugs is thriving due to the multitude of drugs in all stages of development with diverse molecular targets and mechanisms of action.

![Figure 4: Routes of Administration in the Pipeline](image-url)

Source: GBI Research Proprietary Pipeline Products Database
5.1.2.3 Market Size

The growing ACoT and the increase in the treated patient population projected for the forecast period mean that US market is forecast to increase significantly. In 2013, it is forecast to account for XX% of the total key developed markets market at $XX billion, increasing to $XX billion by 2019 at a CAGR of XX%. If it were to peak at $XX billion by 2019, a CAGR of XX% would be expected. This is a scenario in which more expensive pipeline drugs show a strong uptake by the patient population in favor of less expensive, currently available treatments. A lower market size of $XX billion in 2019, which GBI Research considers less likely, is still expected to see a CAGR of XX% (Figure 14, B).

Figure 14: Multiple Sclerosis Market, US, Patient Volumes ('000), Annual Cost of Treatment ($) and Market Size ($bn), 2012–2019

Source: GBI Research
7.3 Market Definition

- The global Multiple Sclerosis market includes the top seven markets of the US, the UK, Germany, France, Spain, Italy and Japan.
- The top five European countries include the UK, Germany, France, Spain and Italy
- Prevalence Population: The prevalence population is the estimated number of people at any given point of time who are affected by Multiple Sclerosis

7.4 Abbreviations

ACoT: Annual Cost of Treatment
ALS: Amyotrophic Lateral Sclerosis
BBB: Blood-Brain Barrier
CAGR: Compound Annual Growth Rate
CD: Cluster of Differentiation
CIS: Clinically Isolated Syndrome
CNS: Central Nervous System
CSF: Cerebrospinal Fluid
DIS: Dissemination In Space
DIT: Dissemination In Time
DMT: Disease-Modifying Therapy
DNA: Deoxyribonucleic Acid
EDSS: Expanded Disability Status Scale
GdE: Gadolinium-enhancing
GPCR: G-Protein Coupled Receptor
HLA: Human Leukocyte Antigen
IFN: Interferon
IFNAR: Interferon Receptor
IL: Interleukin
IV: Intravenous
JAK: Janus Kinase
mAb: Monoclonal Antibody
MBP: Myelin Basic Protein
MRI: Magnetic Resonance Imaging
MS: Multiple Sclerosis
NICE: National Institute for Health and Care Excellence
OCB: Oligoclonal Band
PML: Progressive Multifocal Leukoencephalopathy
POC: Proof-Of-Concept
PPMS: Primary Progressive Multiple Sclerosis
PRMS: Progressive Relapsing Multiple Sclerosis
RRMS: Relapsing-Remitting Multiple Sclerosis
Appendix

SPMS: Secondary Progressive Multiple Sclerosis
S1PR1: Sphingosine-1-Phosphate Receptor type 1
TGFβ: Transforming Growth Factor Beta
Th: T-Helper
UTI: Urinary Tract Infection
VCAM: Vascular Cell Adhesion Molecules

7.5 References


7.6 Methodology

GBI Research’s dedicated research and analysis teams consist of experienced professionals with marketing, market research and consulting backgrounds in the pharmaceutical industry as well as advanced statistical expertise.

GBI Research adheres to the codes of practice of the Market Research Society (www.mrs.org.uk) and the Strategic and Competitive Intelligence Professionals (www.scip.org).

All GBI Research databases are continuously updated and revised.
7.7 Secondary Research

The research process begins with exhaustive secondary research on internal and external sources being carried out to source qualitative and quantitative information relating to each market.

The secondary research sources that are typically referred to include, but are not limited to:

- Company websites, annual reports, financial reports, broker reports, investor presentations and US Securities and Exchanges Commission (SEC) filings
- Industry trade journals, scientific journals and other technical literature
- Internal and external proprietary databases
- Relevant patent and regulatory databases
- National government documents, statistical databases and market reports;
- Procedure registries
- News articles, press releases and web-casts specific to the companies operating in the market

7.8 Therapeutic Landscape

- Revenues for each indication are calculated by utilizing the GBI Research market forecasting model. The global revenue for each indication is the sum value of revenues of all seven countries covered in this report.
- The annual cost of therapy for each indication is arrived at by considering the cost of the drugs, dosage of the drugs and the duration of the therapy.
- The generic share of the market for each indication is obtained by calculating the prescription share for generic drugs and the respective cost of treatment.
- The treatment usage pattern which includes quantitative data on the diseased population, diagnosed population and treated population for an indication, is arrived at by referring to various sources as mentioned below.

GBI Research uses the epidemiology-based treatment flow model to forecast market size for therapeutic indications.
### 7.9 Epidemiology-Based Forecasting

The forecasting model used at GBI Research makes use of epidemiology data gathered from research publications and primary interviews with physicians to represent the treatment flow patterns for individual diseases and therapies. The market for any disease segment is directly proportional to the volume of units sold and the price per unit.

\[
\text{Sales} = \text{Volume of Units sold} \times \text{Price per Unit}
\]

The volume of units sold is calculated on the average dosage regimen for that disease, duration of treatment and number of patients who are prescribed drug treatment (treatment population). Treatment population is calculated as the percentage of population diagnosed with a disease (diagnosis population). The prevalence of a disease (diseased population) is the percentage of the total population that suffers from a disease/condition.

Data on and diagnosis and prescription rates, if unavailable from research publications, are gathered from interviews with physicians and are used to estimate the patient volumes for the disease under consideration. Therapy uptake and compliance data are fitted in the forecasting model to account for patient switching and compliance behavior.

The annual cost of treatment is calculated using product purchase frequency and the average price of the therapy. Product purchase frequency is calculated from the dosage data available for the therapies and drug prices are gathered from public sources. The source for the price of drugs are RxUSA, ZenRx, the UK Prescription Cost Analysis, the British National Formulary and data from the Japan Pharmaceutical Information Center (JAPIC).

The epidemiology-based forecasting model uses a bottom-up methodology and it makes use of estimations in the absence of data from research publications. Such estimations may result in a final market value which is different from the actual value. To correct this ‘gap’ the forecasting model uses ‘triangulation’ with the help of base year sales data (from company annual reports, internal and external databases) and sales estimations.

**Analogous Forecasting Methodology**

Analogous forecasting methodology is used to account for the introduction of new products, patent expiries of branded products and subsequent introduction of generics. Historic data for new product launches and generics penetration are used to arrive at robust forecasts. Increase or decrease of prevalence rates, treatment seeking rate, diagnosis rate and prescription rate are fitted into the forecasting model to estimate market growth rate.

The proprietary model enables GBI Research to account for the impact of individual drivers and restraints in the growth of the market. The year of impact and the extent of impact are quantified in the forecasting model to provide close-to-accurate data sets.
# 7.10 Market Size by Geography

The treatment usage pattern and annual cost of treatment in each country has been factored in while deriving the individual country market size.

## Forecasting Model for Therapeutic Areas

### Figure 35: Multiple Sclerosis Market, Global, GBI Research Market Sizing Model

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<tr>
<th>GBI Research Market Sizing Model</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease Population</strong></td>
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<tr>
<td>General Population: 743,535,048</td>
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<tr>
<td>Qualifying condition 1 (Age/Sex/Occupation etc)</td>
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<tr>
<td>Qualifying condition 2 (Age/Sex/Occupation etc)</td>
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<tr>
<td>Prevalence tissue valve disease: 0.2% 1,784,484</td>
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<tr>
<td>Qualifying condition (complication, severity)</td>
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<tr>
<td>Diseased Population: 1,784,484</td>
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### Treatment Flow Patterns

- **Treatment Seeking Rate (Symptoms/Dis Awareness)**: 89% 1,588,191
- **Diagnosis Rate (Clinical and Diagnostic Tests)**: 75% 1,191,143
- **Prescription Rate (Physician Perception, Treatment Effectiveness)**:
  - Tissue Valve: 70% 833,800
  - Other Treatments for Valve (Surg/med/none) -

### Fulfillment

- Availability: NA
- Willingness to Use (Patient Perceptions): NA
- Ready to Use (Surgery eligibility, Reuse etc): NA

### Affordability at Price

- HE as % of GDP spend
- Average Income (per individual)
- Patient Out-of-pocket Budget (Annual)
  - Budget allocation to onetime surgery
  - Budget allocation to other health needs
- Average Payor Coverage
- Patient Liability
- Target Price (@20% pat liab)
- ASP for Cost of Therapy

### TOTAL PATIENT VOLUMES

- Product Purchase Frequency: 1

### TOTAL UNIT VOLUMES

- Pricing per Unit: $18,000

### Market Value

The above figure represents a typical forecasting model followed in GBI Research. As discussed previously, the model is built on the treatment flow patterns. The model starts with the general population, then the diseased population as a percentage of the general population, and then follows the treatment-seeking population as a percentage of the diseased population and the diagnosed population as a percentage of the treatment-seeking population. Finally, the total volume of units sold is calculated by multiplying the treated population by the average dosage per year per patient.
7.11 Pipeline Analysis

This section provides a list of molecules at various stages in the pipeline for various indications. The list is sourced from internal database and validated for the accuracy of phase and mechanism of action at ClinicalTrials.gov and company websites. The section also includes a list of promising molecules which is narrowed down based on the results of the clinical trials at various stages and the novelty of mechanism of action. The latest press releases issued by the company and news reports are also the source of information for the status of the molecule in the pipeline.

The clinical trial size, duration and failure rate analyses utilize our proprietary databases.

7.13 Disclaimer

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