BioCentury
WEEK OF AUGUST 17, 2015

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SHIFTING MS SPENDING

BY EMILY CUKIER-MEISNER, SENIOR WRITER

Payers are finally getting — and using — the tools to end uninterrupted price increases for multiple sclerosis drugs as a result of an abundance of options, greater willingness to steer prescribing choices, and the entrance of the first generic for the leading treatment in the category.

Specialty drugs are among payers' most expensive and fastest growing categories; however, signs are appearing that MS — one of the most expensive — is about to experience a significant slowdown.

Within the past 10 years, at least seven drugs have been approved to treat relapsing-remitting MS (RRMS). For most of that time new market entries spurred price hikes across the category, rather than driving prices down through competition.

Now, however, level sales growth and a tapering of annual price increases, combined with reduced revenues and guidance from Biogen Inc., suggest this part of the MS market has become a tougher place to play.

The impact looks to be broadening, as well. With more options to offer patients that reduce relapse rates in relapsing-remitting disease, payers are starting to actively manage MS drugs to rein in spending.

In a drug trend report released in March, Express Scripts Holding Co. predicted its growth in spend on all MS medications would fall to low single digits by 2017 from 12.9% in 2014 — close to the 2.6% per year of new MS diagnoses estimated by the National Multiple Sclerosis Society.

The new market reality will be one of slowed revenue growth, bigger rebates and increasing demands for cost-effectiveness data.

MOVES LIKE CAGR

Although Express Scripts declined to be interviewed for this story, in an email the PBM gave BioCentury three reasons for predicting a slowdown in MS spend:

generic competition for Teva Pharmaceutical Industries Ltd.'s Copaxone glatiramer acetate; successful negotiations with manufacturers to mitigate brand inflation; and the expectation that pipeline products won't displace market leaders in the short term.

Express Scripts projected its per-member-per-year spend for MS medications will increase by 11.3% in 2015, 6.5% in 2016 and only 3% in 2017.

It projected spending growth for specialty drugs will tick down only slightly over the same period, increasing by 22.6% in 2015, 22.3% in 2016 and 21.3% in 2017.

Spending in MS has been consistently growing as new entrants set prices at or above existing therapies. Rather than competition driving prices down, the new entrants instead spurred companies with older therapies to boost their prices to catch up (see "Inflection Point?," page 3).

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DAN MENDELSON, AVALERE

The trend hasn't been entirely unmitigated: oral entrants have been more cost conscious about where they fit into the landscape, pricing comparably to injectable products even though the orals offer possible advantages in adherence and efficacy. And in 2012 when Sanofi launched Aubagio teriflunomide, a dihydroorotate dehydrogenase (DHODH) inhibitor, it did so at the low end of the category price range.

According to BioCentury's calculations, prices of MS drugs grew at a compound annual growth rate of 14% from 2004 through 2012. But since then, the CAGR has been 10%, suggesting that brand inflation is already slowing.

Worldwide aggregate sales growth of MS products from four major MS players has remained relatively flat for the past several quarters (see "Slowing Growth," page 4).

Two quarters of sales that missed consensus estimates for Biogen's Tecfidera dimethyl fumarate reinforce the idea that MS companies can no longer take uninterrupted growth for granted.

Tecfidera, which was launched in December 2013, racked up $2.9 billion in worldwide sales in 2014. On the company's 4Q14 earnings call, EVP of Global Commercial Operations Tony Kingsley said the product was on track to become the most prescribed MS therapy worldwide.

Before the company reported 1Q15 earnings, analysts projected Tecfidera sales of $935 million, according to an April 24 note by Sanford Bernstein analyst Geoffrey Porges.

Instead, 1Q15 sales were $825 million.

On the April earnings call, CEO George Scangos attributed the miss to several issues, including "an overall slowing of the MS market," the launch of Biogen's Plegridy peginterferon beta-1a, one reported case of progressive multifocal leukoencephalopathy (PML) and first quarter financial dynamics.

CFO Paul Clancy said those dynamics included one fewer shipping week vs. the previous quarter, higher U.S. gross-to-net adjustments than previous quarters, foreign exchange impact, and sales in Germany after the end of the free-pricing period.

But the trouble continued into 2Q, when revenues for each product within Biogen's MS portfolio came in below the analyst consensus by 4-15%, according to a July 27 note from Porges. Tecfidera itself posted $883 million in sales, 8% below the consensus estimate of $948 million.

Biogen slashed its expected overall revenue growth to 6-8% from 14-16%, primarily due to changes in the estimated Tecfidera trajectory, for which investors docked the company $20 billion in market cap.

On the 2Q earnings call, Kingsley attributed the Tecfidera results to lower than anticipated rates of switching and new patient prescriptions — possibly related to a second PML case — and lower than expected reimbursement in Europe influenced by the lower price of Aubagio.

OPTION OVERRIDE

Payers now have a critical mass of RRMS options available to start managing MS like a traditionally competitive category, and have begun to do so.

Harvard Pilgrim Health Care Inc. CMO Michael Sherman noted that payers had been reluctant to manage their formularies in ways that could restrict the decisions of prescribing neurologists because the available MS products weren't obviously interchangeable and acted upon a complex and unpredictable disease course.

But after seeing MS treatments consistently make the top 10 list of most expensive drugs, Sherman told BioCentury the category now is in the payers' crosshairs, leading them to start managing the drugs more aggressively.

Avalere Health LLC CEO Dan Mendelson said having multiple drugs available gave payers ammunition.

"You've got a number of really strong therapies that are now available to patients with MS, and what has happened is all of these therapies have one way or another landed on a specialty tier," he said.

Some payers have taken the next step beyond tiering: since instituting excluded drug lists, both Express Scripts and CVS Health Corp. have kicked at least one MS injectable interferon off of their formularies. The exclusions have apparently influenced negotiations with companies, as both PBMs have made changes to the category in lists released within the past month.

Express Scripts excluded Novartis AG's Betaseron interferon (IFN) beta-1b in 2014 and 2015, but reinstated it on the 2016 list, which does not exclude any MS drugs.

CVS excluded Merck KGaA's Rebif IFN beta-1a on its 2015 list. For 2016 it reversed course by reinstating Rebif and removing Novartis' Extavia IFN beta-1b and Biogen's Avonex IFN beta-1a and Plegridy.

CVS did not respond to BioCentury's requests for an interview.

Roger Longman, CEO of reimbursement consultancy Real Endpoints LLC, said CVS's decision not to cover Avonex and Plegridy is proof positive that payers have become more aggressive about the rebates they demand, even if it means switching patients who are being stably treated on another drug.

"They've decided not to cover the market leading interferon, and they are willing to move patients who are on those drugs to Rebif. That's a big deal in my view," he said.

Longman expects the payers' actions will help keep price inflation in check.

"What's likely to hold down prices is when payers decide — and I think they're beginning to — that they can in fact move market share from a market leader to a market follower," he said.

Longman also suggested payers may be ready to more aggressively manage other specialty drug classes, such as inflammatory agents and cancer agents.

"Now that they're chipping away at one of the key categories, I would say this is a harbinger of the future," he said.

GLATOPA-YA LESS

Another factor affecting MS spending growth is Novartis' June launch of Glatopa glatiramer acetate, the first generic Copaxone, which the pharma's Sandoz unit developed in partnership with Momenta Pharmaceuticals Inc. Glatopa is already influencing how payers negotiate rebates; however, it will take time for the effects to be reflected in prices.

Copaxone is partially insulated from competition. While it and Glatopa are available as a daily 20 mg injection, in January 2014 Teva launched a 40 mg thrice-weekly formulation that is patent protected.

Longman told BioCentury he expects a long lead-time for generic Copaxone to affect the market, because payers might be reluctant to pressure patients already receiving Copaxone 40 mg to switch.

Sherman agreed it may be difficult to move patients from the 40 mg branded product to Glatopa because the thrice-weekly formulation also has a safety benefit. In the head-to-head GLACIER study, the thrice-weekly version showed a 50% reduction in mean annualized rate of injection-related adverse events compared to the daily 20 mg dose version.

But for some payers — including Harvard Pilgrim — the point may be moot. Sherman said the PBM already receives rebates on the Copaxone 20 mg and 40 mg versions, and that negotiations could make the branded product a better bargain than the generic.

"The takeaway here is rebates are sufficiently impactful that they may lead to a decision to prefer the branded product, including the 40 mg dose, not just because it makes clinical sense, but because it makes sense in terms of value," he said.

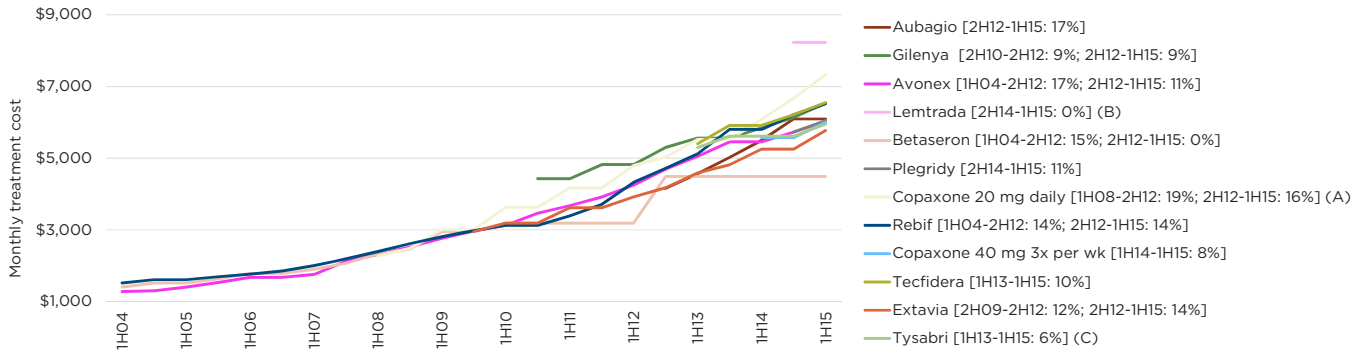
Nevertheless, Sherman expects the availability of a generic Copaxone to have spillover effects on other MS drugs. While he doesn't think it will alter prices at launch — he thinks companies will continue to launch at high prices with the expectation that payers will negotiate more aggressive rebates — he predicted that price increases would flatten.

Teva reported Copaxone sales of $870 million in 2Q15, 12% over 2Q14; however, sales have been choppy for the past two years.

In its 2Q15 results, Teva reported Copaxone had a U.S. market share of 23.8% of new prescriptions and 31.2% of total prescriptions, 68.5% of which were for the 40 mg version.

INFLECTION POINT?

U.S. average wholesale price (AWP) data for MS drugs show double-digit growth rates are giving way to more moderate trajectories. The average compound annual growth rate (CAGR) for MS drugs was 14% for available price data through 2012. Since 2012, the average CAGR has been 10%. Data do not reflect rebates and discounts. The CAGR for specified periods are listed next to each drug in brackets below. (A) Price data not available prior to 2008. (B) Lemtrada is given as an infusion for five days in year one and three days in year two. Monthly cost is based on the first treatment course divided by 12. (C) Price data not available prior to 2013. *Source: Red Book*



On a call to discuss the results, President of Global R&D and CSO Michael Hayden said Novartis' Glatopa had barely cut into Copaxone's franchise, saying the generic had a 1.5% share of the U.S. MS market and less than 5% of the Copaxone market.

On the call, President and CEO of Global Specialty Medicines Rob Koremans said 95% of patients have access to Teva's 40 mg version through payers, and President and CEO Erez Vigodman said payers haven't indicated any change in access for 2016.

Even if Teva preserves market share, it is unlikely to realize the same returns. Among three analysts who projected revenues after Glatopa's launch, all pegged 2014 as Copaxone's peak sales year. The average sales projection dropped from $3.6 billion in 2015 to $1.9 billion in 2020.

Those projections may reflect the threat of additional generic competition. An ANDA for a second generic version from Mylan N.V. and Natco Pharma Ltd. is under FDA review.

Moreover, while Copaxone 40 mg is potentially protected until 2030, Mylan in February filed an *inter partes* review (IPR) challenge to three patents covering low frequency glatiramer acetate therapy.

At least five companies have submitted ANDAs to FDA for generic versions of the thrice-weekly form.

CHANGING EQUATION

The next wave of MS products for RRMS will encounter a market where competitive pressures are fully realized. Companies launching new MS drugs may have to demonstrate value with data that go beyond clinical outcomes, and expect to collect similar data postmarket.

The most advanced of the pending newcomers is Zinbryta daclizumab from AbbVie Inc. and Biogen. The humanized mAb against interleukin-2 (IL-2) receptor alpha chain (CD25) is under FDA and EMA review to treat relapsing forms of MS (see "Up Next in MS," page 5).

Biogen SVP of Global Market Access David Miller declined to discuss the company's pricing or value-demonstration strategies for individual products in its portfolio. But he noted payers have increasingly asked the company to show the value its MS therapies bring in different ways beyond clinical outcomes.

He said Biogen is doing so by collecting quality of life data and utilization of other healthcare services, such as physician visits, hospitalizations, ER visits, and need for healthcare aides.

Miller expects such demands to increase as payers consolidate.

The new expectations aren't limited to payers. Sherman said physicians and hospitals are increasingly asking for such data as they become subject to care delivery systems like accountable care organizations.

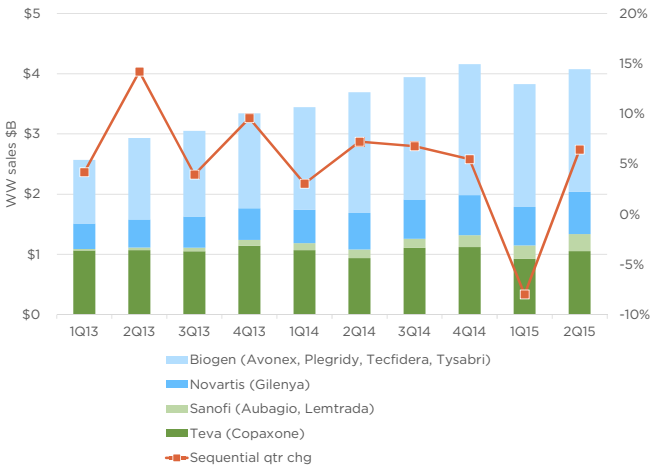
"Before that, they were spending someone else's money. Now they have financial, quality and other incentives — whether that's tiered networks or payments, etc. — to actually want to be cost-effective," he said.

Commitment to postmarket data collection may also be important, as it's not clear whether MS is an indication where data at launch will be sufficiently compelling.

Longman thought it was feasible for premarket data to show a substantial benefit, so long as the magnitude is large. Examples could include greatly reducing the number of disease exacerbations or episodes, or increasing the number of days that patients are well enough to go to work.

SLOWING GROWTH

Aggregate sales of multiple sclerosis drugs from four major players have stalled over the last few quarters, largely due to the recent slowdown in products from **Biogen Inc.** (NASDAQ:BIIB) along with choppy sales of Copaxone glatiramer from **Teva Pharmaceutical Industries Ltd.** (NYSE:TEVA). *Sources: company press releases*



Biogen's Miller cautioned, however, that postmarket data are important to understand how utilization plays out beyond the confines of a clinical trial, whether or not a company is seeking premium pricing.

"Premarket, there's lots of distortion induced because you're adhering to a study protocol. That complicates things when measuring healthcare use," he said.

Miller also said payers would want value data even for products with a new mechanism of action that could confer unprecedented benefits, such as Biogen's BIIB033, an antibody against LINGO-1 (leucine-rich repeat neuronal protein 1) intended to promote remyelination. BIIB033 is in Phase II testing to treat MS.

"Unless we're raising the dead, I think any product is going to have to demonstrate its value, regardless of clinical efficacy or its position in a clinical treatment program," he said.

Sherman said companies seeking to launch therapies at a premium price should expect to land on a high formulary tier, or consider some type of pay-for-performance scenario.

The latter should include outcomes data at launch and also postmarket verification of the claimed benefit.

"If we don't see a reduction in whatever you're claiming, are you going to give us a greater rebate back since we preferred it based on your data? It opens the door to that kind of discussion," he said.

Miller said Biogen has developed its own health economics capabilities to complement its R&D programs, and has already implemented MS pay-for-performance models with payers in the EU.

UP NEXT IN MS

At least eight new compounds are in Phase III or registration to treat multiple sclerosis, led by Zinbryta daclizumab. **AbbVie Inc.** (NYSE:ABBV) said it expects regulatory decisions in the U.S. and EU in 1H16 for Zinbryta. (A) Being acquired by **Celgene Corp.** (NASDAQ:CELG); *Sources: BCIQ: BioCentury Online Intelligence, www.ClinicalTrials.gov, company websites, conference calls*

Company	Product	Description	Indication	MS status (milestone)
AbbVie Inc. (NYSE:ABBV) / **Biogen Inc.** (NASDAQ:BIIB)	Zinbryta daclizumab high-yield process (DAC HYP)	Humanized mAb against IL-2 receptor alpha chain (CD25)	Relapsing MS	Regulatory decisions in U.S. and EU in 1H16
Biogen Inc. (NASDAQ:BIIB) / **Genentech Inc.** / **Roche** (SIX:ROG; OTCQX:RHHBY)	Ocrelizumab (RG1594)	Second-generation humanized mAb against CD20	Relapsing MS; primary progressive MS (PPMS)	Ph III relapsing MS (EU and U.S. filings expected in 1Q16); Ph III PPMS (data 2H15; expected filing 2016)
Medday S.A.S.	MD1003	Concentrated formulation of D-biotin that targets a rate-limiting enzyme in myelination	Progressive MS; visual loss resulting from MS-related optic neuritis	Ph III progressive MS; Ph III MS-related optic neuritis (data 2H15; expected filing 2016)
Receptos Inc. (NASDAQ:RCPT) (A)	Ozanimod	Selective sphingosine 1-phosphate receptor 1 (S1PR1; S1P1; EDG1) modulator	Relapsing MS	Ph III (data 1H17; expected launch 2018)
Active Biotech AB (SSE:ACTI) / **Teva Pharmaceutical Industries Ltd.** (NYSE:TEVA)	Nerventra laquinimod (SAIK-MS)	Oral quinoline-3-carboxamide immunomodulator	Relapsing-remitting MS (RRMS)	Ph III (data mid-2017)
AB Science S.A. (Euronext:AB)	Masitinib	Stem cell factor (SCF) receptor tyrosine kinase (c-Kit; KIT; CD117) inhibitor	PPMS or relapse-free secondary progressive MS (SPMS)	Ph III (interim data 2017)
Actelion Ltd. (SIX:ATLN)	Ponesimod (ACT-128800)	S1PR1 agonist	Relapsing MS	Ph III (complete 2018)
Novartis AG (NYSE:NVS; SIX:NOVN)	Siponimod (BAF312)	Second-generation S1PR1 and S1PR5 agonist	SPMS	Ph III (expected filing ≥2019)

He said providers initially resisted pay-for-performance schemes because of the resources needed to track patients and collect and adjudicate data. Improvements in IT systems have made it easier, Miller said, noting the best systems are run jointly by companies and payers.

"We bring a lot of MS expertise, and they know their systems and clinicians, so it's best to establish a partnership around that," he said.

Miller said the programs collect similar clinical, health economic and patient outcomes data to those that the biotech collects premarket.

Companies developing products to treat progressive forms of MS should also consider how to demonstrate value, though they will be launching into a very different market. The only therapy approved to treat progressive MS is mitoxantrone, a generic chemotherapeutic inhibitor of DNA replication.

Frédéric Sedel, CEO of Medday S.A.S., said his company is collecting data from literature, patient registries and clinical studies to build a cost-savings model for its progressive MS product MD1003, which he said is what EU payers have come to expect.

"If we can demonstrate that the drug works well at the early stages of disease, it totally prevents progression into more severe disability, and maintains patients fully autonomous without need for other help, then we will be in a good position to demonstrate it is cost saving for society," Sedel said.

MD1003 is a concentrated formulation of D-biotin that targets a rate-limiting enzyme in myelination. It is in Phase III testing to treat progressive forms of MS. Medday plans to submit regulatory applications to FDA and EMA in 2016.

Companies may be able to speed demonstration of value by finding biomarkers to predict and track patient responsiveness, but these have remained elusive for MS.

"We have a lot of work going on trying to predict who is going to respond to which MS therapy, from looking at patient characteristics, to clinical characteristics to genetic characteristics. It's been a tough nut to crack," said Miller. bc

COMPANIES AND INSTITUTIONS MENTIONED

AbbVie Inc. (NYSE:ABBV), Chicago, Ill.
Avalere Health LLC, Washington, D.C.
Biogen Inc. (NASDAQ:BIIB), Cambridge, Mass.
CVS Health Corp. (NYSE:CVS), Woonsocket, R.I.
European Medicines Agency (EMA), London, U.K.
Express Scripts Holding Co. (NASDAQ:ESRX), St. Louis, Mo.
Harvard Pilgrim Health Care Inc., Boston, Mass.
Medday S.A.S., Paris, France
Merck KGaA (Xetra:MRK), Darmstadt, Germany
Momenta Pharmaceuticals Inc. (NASDAQ:MNTA), Cambridge, Mass.
Mylan N.V. (NASDAQ:MYL), Canonsburg, Pa.
Natco Pharma Ltd. (BSE:NATCO; NSE:NATCOPHARM), Hyderabad, India
National Multiple Sclerosis Society, New York, N.Y.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Real Endpoints LLC, Westport, Conn.
Sanofi (Euronext:SAN; NYSE:SNY), Paris, France
Teva Pharmaceutical Industries Ltd. (NYSE:TEVA), Petah Tikva, Israel
U.S. Food and Drug Administration (FDA), Silver Spring, Md.

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