Supplementary Appendix

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Investigators

Daniel M. Hartung, PharmD, MPH[1*];
Dennis N. Bourdette, MD, FANA, FAAN[2];
Sharia Ahmed, MPH[1]
Ruth H. Whitham, MD, FAAN[2]

1. Oregon State University / Oregon Health & Science University College of Pharmacy;
   3303 SW Bond Ave;
   CH12C; Portland, OR; 97239
   Phone: 503-706-9192
   Email: hartungd@ohsu.edu

2. Department of Neurology, Oregon Health & Science University, Portland, OR
   Multiple Sclerosis Center of Excellence-West, Veterans Affairs Medical Center, Portland, OR

Segmented Regression Modeling Approach

We compared the median annual cost trends for Betaseron™, Avonex™, and Copaxone™ to contemporaneously approved biologic tumor necrosis factor (TNF) inhibitors etanercept (Enbrel™) and adalimumab (Humira™) using segmented regression analyses.[1] We computed annual costs for TNF inhibitors using the same approach described for MS disease modifying therapies (DMTs) using FDA approved doses for rheumatoid arthritis. Annual costs were estimated quarterly beginning the 4th quarter of 1998 (the quarter Enbrel™ was approved) until the 4th quarter of 2013 (61 total quarters). Four major periods of change were examined: 1) a baseline period preceding the approval of Rebif™ (4th quarter 1998 to 1st quarter 2002), 2) a period from the approval of Rebif™ to the re-introduction of natalizumab (Tysabri™) (2nd quarter 2002 to 2nd quarter 2006), 3) a period from the re-introduction of Tysabri™ to the approval of Gilenya™ (3rd quarter 2006 to 3rd quarter 2010) and 4) a period following the approval of Gilenya™ (4th quarter 2010 to 4th quarter 2013). We selected the re-introduction date for Tysabri™ (June 2006 - 2nd quarter 2006) because it was only available for 2 months before marketing was suspended in 2005 to evaluate the risks of progressive multifocal leukoencephalopathy.

Because initial plot of quarterly data were non-linear, we log-transformed the dependent variable annual cost. The full regression model is as follows:

$$\log(Y_t) = \beta_0 + \beta_1 * Time_t + \beta_2 * Rebif_t + \beta_3 * Time\ Rebif_t + \beta_4 * Tysabri_t + \beta_5 * Time\ Tysabri_t + \beta_6 * Gilenya_t + \beta_7 * Time\ Gilenya_t + \beta_8 * DrugType + \beta_9 * Time_t * DrugType + \beta_{10} * Rebif_t * DrugType + \beta_{11} * Time\ Rebif_t * DrugType + \beta_{12} * Tysabri_t * DrugType + \beta_{13} * Time\ Tysabri_t * DrugType + \beta_{14} * Gilenya_t * DrugType + \beta_{15} * Time\ Gilenya3_t * DrugType + e_t$$

Because the dependent variable was log transformed, the estimated β-coefficients are interpreted as a percent change.[2] Predictor variables were specified as follows:

- $Time_t$ – continuous variable indicating time in quarters since the 4th quarter of 1998
- $Rebif_t$ – indicator variable for the introduction of Rebif™; 1 if the 2nd quarter of 2002 or later, otherwise 0
- $Time\ Rebif_t$ – continuous variable indicating time in quarters since the 2nd quarter of 2002
- $Tysabri_t$ – indicator variable for the re-introduction of Tysabri™; 1 if the 3rd quarter of 2006 or later, otherwise 0
- $Time\ Tysabri_t$ – continuous variable indicating time in quarters since the 3rd quarter of 2006
- $Gilenya_t$ – indicator variable for the introduction of *Gilenya* ™; 1 if the 4th quarter of 2010, otherwise 0
- $Time\ Gilenya_t$ – continuous variable indicating time in quarters since the 4th quarter of 2010
- *DrugType* – indicator variable with 1 being MS DMTs and 0 being TNF inhibitors

Using this model, we estimate quarterly change (period trend) for each period, the change in trend from period to period, and the immediate change (level change) between periods in median costs for DMTs, TNF inhibitors, and their difference derived through the interaction term.

Expontentiated linear combinations of the beta coefficients shown below reflect these estimates.

Estimate	**DMTs**	**TNF inhibitors**	**Difference (interaction)**
Intercept (quarterly cost at time=0)	$\beta_0 + \beta_8$	β_0	β_8
Baseline period trend	$\beta_1 + \beta_9$	β_1	β_9
Rebif™ Introduction			
Level change	$\beta_2 + \beta_{10}$	β_2	β_{10}
Change in period trend	$\beta_3 + \beta_{11}$	β_3	β_{11}
Period trend	$\beta_1 + \beta_3 + \beta_9 + \beta_{11}$	$\beta_1 + \beta_3$	$\beta_9 + \beta_{11}$
Tysabri™ Re-introduction			
Level change	$\beta_4 + \beta_{12}$	β_4	β_{12}
Change in period trend	$\beta_5 + \beta_{13}$	β_5	β_{13}
Period trend	$\beta_1 + \beta_3 + \beta_5 + \beta_9 + \beta_{11} + \beta_{13}$	$\beta_1 + \beta_3 + \beta_5$	$\beta_9 + \beta_{11} + \beta_{13}$
Gilenya™ Introduction			
Level change	$\beta_6 + \beta_{14}$	β_6	β_{14}
Change in period trend	$\beta_7 + \beta_{15}$	β_7	β_{15}
Period trend	$\beta_1 + \beta_3 + \beta_5 + \beta_7 + \beta_9 + \beta_{11} + \beta_{13} + \beta_{15}$	$\beta_1 + \beta_3 + \beta_5 + \beta_7$	$\beta_9 + \beta_{11} + \beta_{13} + \beta_{15}$

Autocorrelation between error terms was assessed using the Durbin-Watson test statistic. If significant autocorrelation was detected ($p<.05$), we adjusted the models with autocorrelation terms selected using a stepwise approach that first fit a model with higher order autocorrelation terms. The least non-significant term was then dropped and the reduced model was successively re-fit until all remaining autocorrelation terms were significant ($p<.05$). All regressions were performed using the PROC AUTOREG in SAS, version 9.2.

Medicaid Rebate Estimation

Pharmaceutical manufacturers must sign rebate contracts with the Centers for Medicare & Medicaid Services (CMS) to obtain coverage for their products within state Medicaid programs. CMS uses Average Manufacturer's Price (AMP) or "best price", the lowest price paid for a drug by any purchaser, to determine Medicaid rebate amounts. Although both AMP and best price are reported to CMS, they are not publically available. AMP has been estimated in OIG reports to be 23% lower than Average Wholesale Price (AWP) for single source branded products.[3] Rebate amounts are derived as the greater of 23% of AMP or the difference between the AMP and the best price.[4] Because best price is not available, we estimated rebate as 23% of AMP.

Annual Cost Estimates

	Pharmacy Acquisition Cost (AWP -12%)	AWP	AMP (AWP - 23%)	US rebate (23% AMP)	Cost net rebate (Acquisition Cost – US rebate)
Betaseron	$61,529	$69,919	$53,838	$12,383	$49,146
Avonex	$62,394	$70,902	$54,595	$12,557	$49,837
Copaxone	$59,158	$67,226	$51,764	$11,906	$47,253
Rebif	$66,394	$75,448	$58,095	$13,362	$53,032
Tysabri	$64,233	$72,992	$56,204	$12,927	$51,306
Extavia	$51,427	$58,440	$44,999	$10,350	$41,078
Gilenya	$63,806	$72,507	$55,831	$12,841	$50,965
Aubagio	$57,553	$65,401	$50,359	$11,582	$45,970
Tecfidera	$63,315	$71,949	$55,401	$12,742	$50,573

Segmented Regression Model Results

ML estimates						
	Variable	Df	Estimate	SE	t-value	p-value
beta0	Intercept	1	9.2567	0.0154	599.87	<.0001
beta1	Time	1	0.0218	0.001805	12.1	<.0001
beta2	Rebif	1	-0.00022	0.0194	-0.01	0.991
beta3	Time Rebif	1	-0.00897	0.002268	-3.95	0.0001
beta4	Tysabri	1	0.003436	0.0186	0.18	0.8537
beta5	Time Tysabri	1	0.000669	0.001918	0.35	0.7281
beta6	Gilenya	1	-0.0213	0.0202	-1.05	0.2947
beta7	Time Gilenya	1	0.0174	0.002436	7.16	<.0001
beta8	DrugType	1	-0.2292	0.0173	-13.24	<.0001
beta9	Time* DrugType	1	-0.00816	0.002037	-4	0.0001
beta10	Rebif * DrugType	1	0.0812	0.0221	3.67	0.0004
beta11	TimeRebif* DrugType	1	0.0276	0.002524	10.92	<.0001
beta12	Tysabri * DrugType	1	-0.0391	0.0212	-1.85	0.0673
beta13	TimeTysabri * DrugType	1	0.012	0.002131	5.64	<.0001
beta14	Gilenya * DrugType	1	-0.00022	0.0231	-0.01	0.9925
beta15	TimeGilenya * DrugType	1	-0.0259	0.002723	-9.53	<.0001

Exponentiated Model Estimates

	DMTs			TNF inhibitors			Difference (interaction)		
	Betas	**Estimates**	**p-value**	**Betas**	**Estimates**	**p-value**	**Betas**	**Estimates**	**P-value**
Intercept‡	$\beta_0 + \beta_8$	$8329	<0.0001	β_0	$10,475	<0.0001	β_8	20.5%	<0.0001
Baseline Trend	$\beta_1 + \beta_9$	1.4%	<0.0001	β_1	2.2%	<0.0001	β_9	–0.8%	0.0001
Rebif™ Introduction									
Level change	$\beta_2 + \beta_{10}$	8.4%	<0.0001	β_2	0.0%	0.991	β_{10}	8.5%	0.0004
Change in period trend	$\beta_3 + \beta_{11}$	1.9%	<0.0001	β_3	-0.9%	0.001	β_{11}	2.8%	<0.0001
Period trend	$\beta_1 + \beta_3 + \beta_9 + \beta_{11}$	3.3%	<0.0001	$\beta_1 + \beta_3$	1.3%	<0.0001	$\beta_9 + \beta_{11}$	2.0%	<0.0001
Tysabri™ Re-introduction									
Level change	$\beta_4 + \beta_{12}$	–3.5%	0.0586	β_4	0.3%	0.8537	β_{12}	–3.8%	0.0673
Change in period trend	$\beta_5 + \beta_{13}$	1.3%	<0.0001	β_5	0.1%	0.7281	β_{13}	1.2%	<0.0001
Period trend	$\beta_1 + \beta_3 + \beta_5 + \beta_9 + \beta_{11} + \beta_{13}$	4.6%	<0.0001	$\beta_1 + \beta_3 + \beta_5$	1.4%	<0.0001	$\beta_9 + \beta_{11} + \beta_{13}$	3.2%	<0.0001
Gilenya™ Introduction									
Level change	$\beta_6 + \beta_{14}$	–2.1%	0.2903	β_6	-2.1%	0.2947	β_{14}	0.0%	0.9925
Change in period trend	$\beta_7 + \beta_{15}$	–0.8%	0.0007	β_7	1.8%	<0.0001	β_{15}	–2.6%	<0.0001
Period trend	$\beta_1 + \beta_3 + \beta_5 + \beta_7 + \beta_9 + \beta_{11} + \beta_{13} + \beta_{15}$	3.7%	<0.0001	$\beta_1 + \beta_3 + \beta_5 + \beta_7$	3.1%	<0.0001	$\beta_9 + \beta_{11} + \beta_{13} + \beta_{15}$	0.6%	0.0183

‡quarterly cost at time=0; exponentiated interaction beta estimates % difference between cost values

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