Supporting material for the paper entitled

# Analysis of the Risks and Benefits of New Chemical Entities Approved by the US Food and Drug Administration (FDA) and Subsequently Withdrawn from the US Market

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## Appendix A – Statistical Methods for Estimating the Uncertainty in the Risk and Benefit Estimates

Risks and benefits of each of the six drugs were estimated to address the primary adverse events and clinical efficacy described in the FDA approval documentation, the approved labeling, meeting transcripts, subsequent withdrawal notices, and the medical literature. A series of assumptions as described in the main paper were then made to quantify risks and benefits in the same units. The following are additional assumptions regarding the uncertainty in these estimates:

- It was generally assumed that integer count data ( $m$ , e.g., the reported numbers of adverse events) were sampled from a Poisson distribution or a Binomial distribution depending on the sample population size ( $N$ ). If $N$ is known and small (e.g., $N < 100$ ) then a Binomial distribution was assumed, otherwise a Poisson distribution was generally assumed.
    - For a Poisson distribution: If a point estimate is equal or proportional to $m$ counts, then the 95% confidence interval of the point estimate is approximately equal to or proportional to $m \pm 1.96\sqrt{m}$ for large $m$ . Otherwise the confidence interval was calculated using the MATLAB poissfit function in the Statistics Toolbox (2006, Ref S1) if $m$ was small.
    - For a Binomial distribution: The confidence interval for the estimated rate $p = m/N$ was calculated using the MATLAB binofit function in the Statistics Toolbox (2006, Ref S1).

– Given two rates $p_1$ and $p_2$ that are estimated from integer count data $m_i$ from a sample of $N_i$ observations such that $p_i = m_i / N_i$ , the standard error of $p_2 - p_1$ was assumed to be (Fleiss 1981, Ref S2),

$$s.e.(p_2 - p_1) = \sqrt{\frac{p_1(1-p_1)}{N_1} + \frac{p_2(1-p_2)}{N_2}} \tag{S1}$$

and the 95% confidence interval for $p_2 - p_1$ was assumed to be

$$p_2 - p_1 \pm 1.96\ s.e.(p_2 - p_1) \tag{S2}$$

– It was generally assumed that the uncertainty in the estimates of the various terms used to estimate the risks and benefits are uncorrelated. It was not assumed in general that the uncertainty was symmetric.

– Therefore the lower bounds (LB), point estimate (PE), and upper bounds (UB) for sum of uncorrelated terms were assumed to be equal to

$$\begin{aligned} LB_{sum} &= PE_{sum} - \sqrt{\sum_k (LB_k - PE_k)^2} \\ PE_{sum} &= \sum_k PE_k \\ UB_{sum} &= PE_{sum} + \sqrt{\sum_k (UB_k - PE_k)^2} \end{aligned}$$

– The lower bounds, point estimate, and upper bounds for the product of uncorrelated terms were assumed to be approximately equal to:

$$LB_{product} = PE_{product} - PE_{product}\sqrt{\sum_k \left(\frac{LB_k - PE_k}{PE_k}\right)^2}$$

$$PE_{product} = \prod_k PE_k$$

$$UB_{product} = PE_{product} + PE_{product}\sqrt{\sum_k \left(\frac{UB_k - PE_k}{PE_k}\right)^2}$$

This is an approximation is based on the chain rule.

– The uncertainty in the risk and benefit estimates due to the uncertainty in the mean remaining life expectancy <u>at a given age</u> is small compared to the other sources of uncertainty and can be neglected. See Arias et al. (2008, Ref S3) Table 11.

## Appendix B – Estimated risks and benefits of the six individual drugs corresponding to FDA action

The risks and benefits corresponding to each FDA decision to approve each drug or subsequent market withdrawal were estimated as described in in this Appendix. The specific approaches used to estimate the risks and benefits of each drug and action vary depending on the nature of the risks and benefits, available information, and necessary assumptions. The supporting references for each drug are numbered in chronological order because the timing of the available information may be relevant to the FDA action and this analysis[1]. Some of the risk and benefit analyses use life expectancy information from Arias et al. (2008, Ref S3). It was assumed that the life expectancy was relatively constant and known to the FDA in the time period covered by this analysis. The results are summarized in Table 1 in the main paper.

### *Baycol (cerivastatin sodium)*

This section describes the estimated risks and benefits of Baycol based on information in Refs S3, S4 through S16, S18, and S25. The calculation steps and values are provided in Table S1 through Table S6 and the supporting sources and notes.

Baycol was originally approved in June 1997 as an adjunct to diet for the reduction of elevated total and low-density lipoprotein (LDL) cholesterol levels in patients with primary hypercholesterolemia and mixed dyslipidemia (NDA 20-740, Refs S8 and S9).

[1] The date for the NDA approval histories is the date of the original NDA approval for the purposes of the chronological ordering.

The estimated risk of Baycol at the time of initial approval was quantified in terms of QALY lost based on the probabilities of the adverse events listed in the approval documentation (e.g., Ref S9, Medical Reviews, Part 2, PDF page 48). Most of the adverse events (AEs) listed were assumed to have a relatively small effect on the quality of life when compared with the primary AEs of greatest clinical concern, myalgia and myopathy. The QALY disutility factor and loss duration for myalgia were assumed to be 0.2 life units and 0.25 years respectively based Erickson et al (2013, Ref S15). The disutility factor for myopathy was assumed to be twice that of myalgia, and the loss duration was assumed to be 0.25 years. At the time of the original approval, rhabdomyolysis had been observed with other statins (HMG-CoA reductase inhibitors), but not for Baycol. The resulting estimated risk of Baycol was **0.00060 (-0.00025, 0.00145)** QALY lost per patient (see Table S1).

The estimated benefit of Baycol at the time of approval was quantified in terms of QALY gained based on patient cholesterol response information in the approval documentation (e.g., Medical Reviews, Part 1, PDF pages 40-42), and corresponding patient response and estimated benefits information for a related drug, pravastatin, reported by Shepherd *et al* (1995, Ref S7). This approach was used because the benefits of pravastatin in preventing non-fatal myocardial infarction and death from all cardiovascular causes could be estimated in terms of QALY gained, as an intermediate step toward estimating the corresponding benefits of Baycol. This approach is based on the assumption that the benefits of Baycol could be estimated by linearly interpolating the benefits of Pravastatin based on the Total-C, LDL-C, and the inverse of the HDL-C responses. This approach is justified because the Baycol labeling indicated that "… *epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C*", and since

the ranges in Total-C, LDL-C, and HDL-C changes due to Baycol and pravastatin were very similar in magnitude and therefore suitable for linear interpolation. It was further assumed that the benefit duration (*Tq*) for deaths and non-fatal myocardial infarctions prevented was equal to the patient life expectancy at the time of the prevented event. This benefit duration was assumed to be equal to the time the treatment began minus 1/2 the treatment duration, assuming that the probably of death or non-fatal myocardial infarction per unit of time is constant during the treatment duration. The age when treatment began was assumed to be 55.2 (44.2 to 66.2) years based on the WOSCOPS trials (Shepherd et al. 1995, Ref S7). The average treatment duration was assumed to be 4.9 years based on the same study. Therefore the benefit time duration (*Tq*) was assumed to be 25.6 (17.1 to 35.4) years based on the U.S. life expectancy in 1999-2001 (Arias et al., 2008, Ref S3), minus 4.9/2 years. The resulting estimated average benefit for the 0.05, 0.1, 0.2 and 0.3 mg doses of Baycol was **0.19525 (0.04584, 0.43194)** QALY gained per patient (see Table S2 and Table S3).

Baycol was voluntarily withdrawn from the US market in August 2001 based on emerging post-marketing safety information demonstrating an excess risk of rhabdomyolysis when compared with other approved statins (FDA Press Office, 2001, Ref S12). The estimated risk of Baycol at the time of market withdrawal was quantified, based on AE information in the final FDA-approved labeling (NDA 20-740/S019, Ref S11) and available information on the risk of rhabdomyolysis reported subsequently in the medical literature (Staffa et al. (2002, Ref S13) and Graham et al. (2004, Ref S14). In this analysis, it was assumed that (1) AEs reported to the FDA's Adverse Event Reporting System (AERS) are under-reported, with a reporting rate of 10% (1% to 100%) (Memo from Mackey to Raczkowski dated March 26, 2002 (NDA 21-107/S005, Ref S25, PDF page 464), which is turn was based on Rogers et al. (1988, Ref S5) and

Scott et al. (1987, Ref S4); (2) this under-reporting rate was known to the FDA at the time of Baycol withdrawal (memo from Graham (FDA) dated April 17, 1996 (NDA 16-832/S013, Ref S18, PDF pages 34-35), with Staffa et al. (2002, Ref S13) assuming a reporting rate of 1%. Based on these assumptions, the estimated risk of Baycol was 0.03898 (0.00629, 0.90203) QALY lost per patient, or approximately 65 times the risk at the time of initial approval (see Table S4). Moreover, based on information reported by Staffa et al. (2002, Ref S13) and Graham et al. (2004, Ref S14), the estimated risks of Baycol due to rhabdomyolysis (0.03848 (0.00576, 0.89239) QALY lost per patient) were nearly 100 times higher than for Pravastatin (0.00039 (0.00000, 0.02414) QALY lost per patient). Therefore the incremental risk of Baycol compared to Pravastatin is **0.03809 (0.00306, 0.89168)** QALY lost per patient (see Table S5). In contrast, the average estimated benefit of Baycol at the time of market withdrawal (based on the updated cholesterol response information for the 0.2, 0.3, 0.4 and 0.8 mg dose levels in the final FDA-approved labeling (NDA 20-740/S019, Ref S11) was 0.29421 (0.05807, 0.53459) QALY gained per patient, versus a corresponding estimated benefit for pravastatin of 0.23180 (0.05923, 0.41956) QALY gained per patient, suggestive of only a negligible difference in efficacy between the two drugs (i.e., the incremental benefit is **0.06241 (-0.0116, 0.11503)** QALY gained per patient) (see Table S6).

Table S1. Estimated Risk of Baycol (cerivastatin sodium tablets, 0.05, 0.1, 0.2 and 0.3 mg) corresponding to the FDA decision to approve NDA 20-740 on 1997-06-26.

| (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) | (I) | (J) | (K) | (L) | (M) | (N) | (O) | (P) | (Q) | (R) | (S) | (T) | (U) | (V) | (W) | (X) | (Y) | (Z) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Adverse Event | Baycol (0.05, 0.1, 0.2 and 0.3 mg) | | | | | Placebo | | | | | Estimated Net Increase in Risk per Patient due to Baycol | | | | Assumed QALY Disuse Factor | | | Assumed Loss Duration (years) | | | Estimated Risk (QALY Lost per Cerivastatin Patient) | | | | |
| | Number of | | Estimated Risk | | | Number of | | Estimated Risk | | | | | | | | | | | | | | | | | |
| | Patients | Events =(B)x(D) | PE | LB | UB | Patients | Events =(G)x(I) | PE | LB | UB | PE =(D)-(I) | SE of PE | LB | UB | PE | LB | UB | PE | LB | UB | PE =(L)x(P)x(S) | LB-PE | LB =(V)+(W) | UB-PE | UB =(V)+(Y) |
| | | | | | | | | | | | | | | | | | | | | | | | | | |
| Abdominal pain | 1063 [a] | 41 [b] | 3.9% [a] | 2.8% [c] | 5.2% [c] | 247 [a] | 9 [b] | 3.6% [a] | 1.7% [c] | 6.8% [c] | 0.3% | 1.33% [d] | -2.30% [e] | 2.90% [e] | [f] | [f] | [f] | [f] | [f] | [f] | | | | | |
| Asthenia | 1063 [a] | 34 [b] | 3.2% [a] | 2.2% [c] | 4.4% [c] | 247 [a] | 7 [b] | 2.8% [a] | 1.1% [c] | 5.8% [c] | 0.4% | 1.18% [d] | -1.91% [e] | 2.71% [e] | [f] | [f] | [f] | [f] | [f] | [f] | | | | | |
| Leg pain | 1063 [a] | 26 [b] | 2.4% [a] | 1.6% [c] | 3.6% [c] | 247 [a] | 3 [b] | 1.2% [a] | 0.3% [c] | 3.5% [c] | 1.2% | 0.84% [d] | -0.44% [e] | 2.84% [e] | [f] | [f] | [f] | [f] | [f] | [f] | | | | | |
| Diarrhea | 1063 [a] | 48 [b] | 4.5% [a] | 3.3% [c] | 5.9% [c] | 247 [a] | 9 [b] | 3.6% [a] | 1.7% [c] | 6.8% [c] | 0.9% | 1.35% [d] | -1.74% [e] | 3.54% [e] | [f] | [f] | [f] | [f] | [f] | [f] | | | | | |
| Arthralgia | 1063 [a] | 78 [b] | 7.3% [a] | 5.8% [c] | 9.1% [c] | 247 [a] | 11 [b] | 4.5% [a] | 2.2% [c] | 7.8% [c] | 2.8% | 1.54% [d] | -0.22% [e] | 5.82% [e] | [f] | [f] | [f] | [f] | [f] | [f] | | | | | |
| Myalgia | 1063 [a] | 23 [b] | 2.2% [a] | 1.4% [c] | 3.2% [c] | 247 [a] | 3 [b] | 1.2% [a] | 0.3% [c] | 3.5% [c] | 1.0% | 0.83% [d] | -0.62% [e] | 2.62% [e] | 0.2 [g] | 0.1 [g] | 0.3 [g] | 0.25 [h] | 0.25 [i] | 0.25 [i] | 0.00050 | -0.00085 [j] | -0.00035 | 0.00085 [k] | 0.00135 |
| Insomnia | 1063 [a] | 22 [b] | 2.1% [a] | 1.3% [c] | 3.1% [c] | 247 [a] | 3 [b] | 1.2% [a] | 0.3% [c] | 3.5% [c] | 0.9% | 0.82% [d] | -0.71% [e] | 2.51% [e] | [f] | [f] | [f] | [f] | [f] | [f] | | | | | |
| Sinusitis | 1063 [a] | 78 [b] | 7.3% [a] | 5.8% [c] | 9.1% [c] | 247 [a] | 14 [b] | 5.7% [a] | 3.1% [c] | 9.3% [c] | 1.6% | 1.68% [d] | -1.69% [e] | 4.89% [e] | [f] | [f] | [f] | [f] | [f] | [f] | | | | | |
| Cough increased | 1063 [a] | 27 [b] | 2.5% [a] | 1.7% [c] | 3.7% [c] | 247 [a] | 5 [b] | 2.0% [a] | 0.7% [c] | 4.7% [c] | 0.5% | 1.01% [d] | -1.48% [e] | 2.48% [e] | [f] | [f] | [f] | [f] | [f] | [f] | | | | | |
| Bronchitis | 1063 [a] | 26 [b] | 2.4% [a] | 1.6% [c] | 3.6% [c] | 247 [a] | 4 [b] | 1.6% [a] | 0.4% [c] | 4.1% [c] | 0.8% | 0.93% [d] | -1.02% [e] | 2.62% [e] | [f] | [f] | [f] | [f] | [f] | [f] | | | | | |
| Myopathy | | | | | | | | | | | 0.1% [l] | | 0.00% [l] | 0.20% [l] | 0.4 [m] | 0.2 [m] | 0.6 [m] | 0.25 [h] | 0.25 [i] | 0.25 [i] | 0.00010 | -0.00011 [j] | -0.00001 | 0.00011 [k] | 0.00021 |
| Rhabdomyolysis | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Total** | | | | | | | | | | | | | | | | | | | | | **0.00060** [n] | -0.00085 [o] | **-0.00025** | 0.00085 [p] | **0.00145** |

Sources and Notes

LB Lower bounds of the estimate
PE Point estimate
SE Standard error of the point estimate
UB Upper bounds of the estimate
QALY Quality-adjusted life-years

[a] NDA 20-740 (Ref S9), Medical Review(s), Part 2, PDF page 48. Also ibid., Clinical Pharmacology Biopharmaceutics Review(s), Part 2, PDF pages 23-24. Only the Adverse Events where the Baycol percentage is greater than the Placebo percentage are listed.
[b] =Number of Patients x Estimated Risk (i.e., =(B)x(D) or =(G)x(I)).
[c] Calculated using the Matlab Statistics Toolbox Binofit function (Ref S1).
[d] =SQRT( (D)x(1-(D))/(B) + (I)x(1-(I))/(G) ) according to Eqn (2.13) in Fleiss (1981, Ref S2).
[e] =(L)±1.96x(M). See Eqn (7.6) in Fleiss (1981, Ref S2).
[f] Assumed to be negligible.
[g] Assumed to be equal to 1 - the QALY utility value while experiencing myalgia assumed by Erickson et al. (2013, Ref S15) Table 1 (0.80 (0.70,0.90)). This assumes the quality of life utility of the patient before treatment is 1.
[h] Assumed value based on 'Patients who developed myalgias incurred a ... 3-month quality-of-life decrement due to the muscle pain' (Erickson et al., 2013, Ref S15, page 1251).
[i] Assumed equal to the point estimate.
[j] =-SQRT( (((N)-(L))x(P)x(S))^2 + ((L)x((Q)-(P))x(S))^2 + ((L)x(P)x((T)-(S)))^2 ), based on the assumption that the uncertainties in the terms are uncorrelated.
[k] =SQRT( (((O)-(L))x(P)x(S))^2 + ((L)x((R)-(P))x(S))^2 + ((L)x(P)x((U)-(S)))^2 ), based on the assumption that the uncertainties in the terms are uncorrelated.
[l] Assumed values based on NDA 20-740 (Ref S9), Medical Review(s), Part 2, PDF page 41, which indicates that Myopathy 'was rare (<0.2%) in U.S. cerivastatin clinical trials'. Also ibid., Clinical Pharmacology Biopharmaceutics Review(s), Part 2, PDF pages 17-18.
[m] Assumed to be equal to 2 x the QALY disutility value while experiencing myalgia assumed by Erickson et al. (2013, Ref S15).
[n] =column total.
[o] =-SQRT(SUM((W)^2)), based on the assumption that the uncertainties in the estimated risks for each adverse event are uncorrelated.
[p] =SQRT(SUM((Y)^2)), based on the assumption that the uncertainties in the estimated risks for each adverse event are uncorrelated.

Table S2. Estimated Benefit of Pravastatin, corresponding to the FDA decision to approve Baycol (cerivastatin sodium) on 1997-02-06 and subsequent US market withdrawal on 2001-08-08.

| (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) | (I) | (J) | (K) | (L) | (M) | (N) | (O) | (P) | (Q) | (R) | (S) | (T) | (U) | (V) | (W) | (X) | (Y) | (Z) | (AA) | (AB) | (AC) | (AD) | (AE) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Adverse Event Prevented | Pravastatin | | | | | Placebo | | | | | Estimated Net Decrease in Risk per Patient due to Pravastatin | | | | Patient Age at the Start of the Treatment (Years) | | | | Treatment Duration (Yr) | Assumed QALY Disuse Factor | | | Assumed Benefit Duration (years) | | | Estimated Benefit (QALY Gained per Pravastatin Patient) | | | | |
| | Number of | | Estimated Risk | | | Number of | | Estimated Risk | | | | | | | | | | | | | | | | | | | | | | |
| | Patients | Events | PE =(C)/(B) | LB | UB | Patients | Events | PE =(H)/(G) | LB | UB | PE =(I)-(D) | SE of PE | LB | UB | PE | SD | LB | UB | PE | PE | LB | UB | PE | LB | UB | PE =(L)x(U)x(X) | LB-PE | LB =(AA)+(AB) | UB-PE | UB =(AA)+(AD) |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Death from all cardiovascular causes | 3302 [a] | 50 [a] | 1.5% | 1.13% [b] | 1.99% [b] | 3293 [a] | 73 | 2.2% [a] | 1.74% [b] | 2.78% [b] | 0.7% | 0.33% [c] | 0.05% [d] | 1.36% [d] | 55.2 [e] | 5.5 [e] | 66.0 [f] | 44.4 [f] | 4.9 [g] | 1 [h] | 1 [i] | 1 [i] | 23.16 [k] | 14.6 [k] | 32.79 [k] | 0.16272 [l] | -0.16275 [m] | -0.00003 | 0.165675 [n] | 0.32840 |
| Non-fatal myocardial infarction | 3302 [a] | 143 [a] | 4.3% | 3.66% [b] | 5.08% [b] | 3293 [a] | 204 | 6.2% [a] | 5.40% [b] | 7.07% [b] | 1.9% | 0.55% [c] | 0.79% [d] | 2.94% [d] | 55.2 [e] | 5.5 [e] | 66.0 [f] | 44.4 [f] | 4.9 [g] | 0.16 [j] | 0.085 [j] | 0.33 [j] | 23.16 [k] | 14.6 [k] | 32.79 [k] | 0.06908 [l] | -0.05739 [m] | 0.01169 | 0.088348 [n] | 0.15743 |
| Other | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Total** | | | | | | | | | | | | | | | | | | | | | | | | | | **0.23180** [o] | -0.17257 [p] | **0.05923** | 0.187759 [q] | **0.41956** |

Sources and Notes

HDL-C High density lipoprotein cholesterol
LB Lower bounds of the estimate
LDL-C Low density lipoprotein cholesterol
PE Point estimate
QALY Quality-adjusted life-years
SD Standard deviation of the data
SE Standard error of the point estimate
Total-C Total cholesterol
UB Upper bounds of the estimate
WOSCOPS West of Scotland Coronary Prevention Study

[a] Shepherd et al. (1995, Ref S7), page 1303, Table 2.
[b] Calculated using the Matlab Statistics Toolbox Binofit function (Ref S1).
[c] =SQRT( (D)x(1-(D))/(B) + (I)x(1-(I))/(G) ) according to Eqn (2.13) in Fleiss (1981, Ref S2).
[d] =(L)±1.96x(M). See Eqn (7.6) in Fleiss (1981, Ref S2).
[e] The average age of the patients in the Shepherd et al. (1995, Ref S7) study was 55.2 years with a 5.5 year standard deviation.
[f] =(P)±1.96x(Q).
[g] Shepherd et al. (1995, Ref S7), page 1303.
[h] Based on the assumption that the patient utility before treatment is 1. The utility value for death is 0 by definition.
[i] Assumed equal to the point estimate.
[j] Assumed to be equal to 1-average of the utility values reported in Tsevat et al. (1993, Ref S6) (0.88 (0.84,0.93)), and Erickson et al. (2013, Ref S15) Table 1 (0.80 (0.50,0.90)). Note this assumes the patient utility before the treatment is 1.
[k] Assumed equal to the life expectancy of the patient at the time the adverse event would have occurred (which depends on the age of the patient at the start of the treatment) minus 1/2 the treatment duration. This assumes that the probability the avoided event would have occurred was constant. during the treatment duration. Therefore the PE, LB, and UB values were based on the average life expectancy reported in Arias et al. (2008, Ref S3) Table 1 for the ages values rounded to 55, 66, and 44 years respectively, minus (T)/2.
[l] =(L)x(U)x(X).
[m] =-SQRT( (((N)-(L))x(U)x(X))^2 + ((L)x((V)-(U))x(X))^2 + ((L)x(U)x((Y)-(X)))^2 ), based on the assumption that the uncertainty in the terms are uncorrelated.
[n] =SQRT( (((O)-(L))x(U)x(X))^2 + ((L)x((W)-(U))x(X))^2 + ((L)x(U)x((Z)-(X)))^2 ), based on the assumption that the uncertainty in the terms are uncorrelated.
[o] =column total
[p] =-SQRT(SUM((AB)^2)), based on the assumption that the uncertainties in the estimated benefits for each adverse event prevented are uncorrelated.
[q] =SQRT(SUM((AD)^2)), based on the assumption that the uncertainties in the estimated benefits for each adverse event prevented are uncorrelated.

Table S3. Estimated Benefit of Baycol (cerivastatin sodium tablets, 0.05, 0.1, 0.2 and 0.3 mg) corresponding to the FDA decision to approve NDA 20-740 on 1997-06-26.

Response in Patients with Primary Hypercholesterolemia, Mean Percent Change from Baseline after 24 Weeks

| (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) | (I) | (J) | (K) | (L) | (M) | (N) | (O) | (P) | (Q) | (R) | (S) | (T) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dosage | N | Total-C | | | LDL-C | | | HDL-C | | | Triglycerides | | | Relative Effect | | | Estimated Benefit (QALY Gained per Statin Patient) | | |
| | | Change | Net Change | Relative Effect | Change | Net Change | Relative Effect | Change | Net Change | Relative Effect | Change | Net Change | Relative Effect | | | | | | |
| | | PE | PE | PE | PE | PE | PE | PE | PE | PE | PE | PE | PE | PE =(H) | LB | UB | PE | LB | UB |
| Placebo | 152 [a] | 1.4% [b] | | | 1.2% [c] | | | 3.1% [d] | | | 2.0% [e] | | | | | | | | |
| Baycol, 0.05 mg once daily | 158 [a] | -9.4% [b] | -10.8% [f] | 0.54 [h] | -13.3% [c] | -14.5% [f] | 0.56 [h] | 5.7% [d] | 2.6% [f] | 1.02 [i] | -6.1% [e] | -8.1% [f] | 0.68 [j] | 0.56 [k] | 0.54 [l] | 1.02 [l] | 0.12927 [m] | 0.03198 [m] | 0.42938 [m] |
| Baycol, 0.1 mg once daily | 154 [a] | -12.1% [b] | -13.5% [f] | 0.68 [h] | -18.0% [c] | -19.2% [f] | 0.74 [h] | 7.4% [d] | 4.3% [f] | 1.01 [i] | -5.3% [e] | -7.3% [f] | 0.61 [j] | 0.74 [k] | 0.68 [l] | 1.01 [l] | 0.17118 [m] | 0.03998 [m] | 0.42238 [m] |
| Baycol, 0.2 mg once daily | 159 [a] | -16.5% [b] | -17.9% [f] | 0.90 [h] | -24.0% [c] | -25.2% [f] | 0.97 [h] | 9.8% [d] | 6.7% [f] | 0.98 [i] | -9.7% [e] | -11.7% [f] | 0.98 [j] | 0.97 [k] | 0.90 [l] | 0.98 [l] | 0.22467 [m] | 0.05301 [m] | 0.41288 [m] |
| Baycol, 0.3 mg once daily | 154 [a] | -18.9% [b] | -20.3% [f] | 1.02 [h] | -27.5% [c] | -28.7% [f] | 1.10 [h] | 9.6% [d] | 6.5% [f] | 0.99 [i] | -12.0% [e] | -14.0% [f] | 1.17 [j] | 1.10 [k] | 0.99 [l] | 1.10 [l] | 0.25587 [m] | 0.05840 [m] | 0.46313 [m] |
| Baycol, average | | | | | | | | | | | | | | 0.84 [n] | 0.77 [n] | 1.03 [n] | **0.19525** [n] | **0.04584** [n] | **0.43194** [n] |
| | | | | | | | | | | | | | | | | | | | |
| Pravastatin, 40 mg each evening | | | -20% [g] | 1.00 [h] | | -26% [g] | 1.00 [h] | | 5% [g] | 1.00 [i] | | -12% [g] | 1.00 [j] | 1.00 [k] | 1.00 [l] | 1.00 [l] | 0.23180 [o] | 0.05923 [o] | 0.41956 [o] |

Sources and Notes

HDL-C High density lipoprotein cholesterol
LB Lower bounds of the estimate
LDL-C Low density lipoprotein cholesterol
PE Point estimate
QALY Quality-adjusted life-years
Total-C Total cholesterol
UB Upper bounds of the estimate

[a] NDA 20-740 (Ref S9), Statistical Reviews, Part 1, PDF page 7, Table 5, Study 124, Intent-to-treat population.

[b] NDA 20-740 (Ref S9), Medical Reviews, Part 1, PDF pages 40-41, Table 7.2.6, Study 124; also Statistical Reviews, Part 1, PDF page 8, Table 6, Study 124.

[c] NDA 20-740 (Ref S9), Medical Reviews, Part 1, PDF page 42, Table 7.2.6, Study 124; also Statistical Reviews, Part 1, PDF page 8, Table 7, Study 124.

[d] NDA 20-740 (Ref S9), Medical Reviews, PDF page 42, Table 7.2.6, Study 124; also Statistical Reviews, Part 1, PDF page 9, Table 8, Study 124.

[e] NDA 20-740 (Ref S9), Medical Reviews, Part 1, PDF page 43, Table 7.2.6, Study 124; also Statistical Reviews, Part 1, PDF page 9, Table 9, Study 124.

[f] =Baycol Change-Placebo Change.

[g] Results of the West of Scotland Coronary Prevention Study (WOSCOPS) reported in Shepherd et al. (1995, Ref S7) page 1304.

[h] =Net Change/Pravastatin Net Change, based on the statement in NDA 20-740/S003 (Ref S10, PDF page 6) that "Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C."

[i] =(1+Pravstatin Net Change)/(Net Change), based on the statement in NDA 20-740/S003 (Ref S10, PDF page 6) that "Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C."

[j] =Net Change/Pravastatin Net Change. This value is for comparison purposes only.

[k] Assume that the LDL-C reduction (H) has the main effect on QALY benefit.

[l] Assume the lower and upper bounds for the relative effect are equal to the minimum and maximum values for (E), (H) and (K).

[m] =Relative Effect (e.g., (O) ((P),(Q)) ) x Estimated Benefit ( (R) ((S),(T)) ) for Pravastatin. This assumes that the QALY benefits vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C.

[n] =average value for the 0.05, 0.1, 0.2, and 0.3 mg Baycol doses.

[o] From columns (AA), (AC) and (AE) of Table S2. Based on reductions in death from all cardiovacular causes and nonfatal myocardial infarction observed in WOSCOPS reported in Shepherd et al. (1995, Ref S7) Table 2.

Note that NDA 20-740 (Ref S9) indicated in the proposed labeling (e.g., Medical Reviews, Part 2, PDF page 40) that:

*"The effect of cerivastatin-induced changes in lipoprotein levels, including reduction of serum cholesterol, on cardiovascular morbidity or mortality has not been established."*

ibid., Medical Reviews, Part 2, further states on PDF page 33 that (emphasis added):

*"The inclusion of broad summary statements addressing certain demonstrated clinical benefits of lipid lowering, of summary data from the LRC-CPPT using cholestyramine, and of references to the 4S and WOSCOPS trials and their results in the label for cerivastatin should be deleted Such information is not essential for the safe and effective use of the drug. Furthermore, the inclusion of this information implies effectiveness of cerivastatin not demonstrated in well-controlled trials using the drug. At this point in time, there is sufficient general knowledge as to the presumed benefits of cholesterol lowering such that no* ***explicit*** *rationale for treatment need be provided in labeling."*

It is however assumed the results of the WOSCOPS did provide some implicit rationale for the benefits in the FDA decision making even if these benefits were not explicitly indicated on the labeling.

Table S4. Estimated Risk of Baycol (cerivastatin sodium tablets, 0.2, 0.3, 0.4 and 0.8 mg) corresponding to the US market withdrawal on 2001-08-08.

| (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) | (I) | (J) | (K) | (L) | (M) | (N) | (O) | (P) | (Q) | (R) | (S) | (T) | (U) | (V) | (W) | (X) | (Y) | (Z) | (AA) | (AB) | (AC) | (AD) | (AE) | (AF) | (AG) | (AH) | (AI) | (AJ) | (AK) | (AL) | (AM) | (AN) | (AO) | (AP) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Adverse Event | Clinical Studies | | | | | | | | | | Postmarketing Data | | | | | | | | | | | | | | | | Combined Estimates | | | | | | | | | | | | | | |
| | Baycol (0.2, 0.3, 0.4 and 0.8 mg) | | | | | Placebo | | | | | Estimated Number of | | | Number of Reported | Estimated Adverse Event Reporting Rate | | | Estimated Risk per Person-Year of Treatment | | | Assumed Age to Begin Treatment (Years) | | | Assumed Treatment Duration (years) | | | Estimated Net Increase in Risk per Patient due to Baycol | | | | Assumed QALY Disuse Factor | | | Assumed Loss Duration (years) | | | Estimated Risk (QALY Lost per Cerivastatin Patient) | | | | |
| | Number of | | Estimated Risk | | | Number of | | Estimated Risk | | | Prescriptions | Prescriptions per PY | Person-Years | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Patients | Events =(B)x(D) | PE | LB | UB | Patients | Events =(G)x(I) | PE | LB | UB | PE | PE | PE =(L)/(M) | Events | PE | LB | UB | PE =(O)/((N)x(P)) | LB | UB | PE | LB | UB | PE | LB | UB | PE | SE of PE | LB | UB | PE | LB | UB | PE | LB | UB | PE | LB-PE | LB | UB-PE | UB |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Asthenia | 2231 [a] | 76 [b] | 3.4% [a] | 2.7% [c] | 4.2% [c] | 702 [a] | 15 [b] | 2.1% [a] | 1.2% [c] | 3.5% [c] | | | | | | | | | | | | | | | | | 1.3% [d] | 0.66% [e] | 0.00% [f] | 2.60% [f] | [g] | [g] | [g] | [g] | [g] | [g] | | | | | |
| Chest pain | 2231 [a] | 45 [b] | 2.0% [a] | 1.5% [c] | 2.7% [c] | 702 [a] | 13 [b] | 1.8% [a] | 1.0% [c] | 3.1% [c] | | | | | | | | | | | | | | | | | 0.2% [d] | 0.58% [e] | -0.94% [f] | 1.34% [f] | [g] | [g] | [g] | [g] | [g] | [g] | | | | | |
| Leg pain | 2231 [a] | 49 [b] | 2.2% [a] | 1.6% [c] | 2.9% [c] | 702 [a] | 10 [b] | 1.4% [a] | 0.7% [c] | 2.6% [c] | | | | | | | | | | | | | | | | | 0.8% [d] | 0.54% [e] | -0.26% [f] | 1.86% [f] | [g] | [g] | [g] | [g] | [g] | [g] | | | | | |
| Constipation | 2231 [a] | 49 [b] | 2.2% [a] | 1.6% [c] | 2.9% [c] | 702 [a] | 14 [b] | 2.0% [a] | 1.1% [c] | 3.3% [c] | | | | | | | | | | | | | | | | | 0.2% [d] | 0.61% [e] | -1.00% [f] | 1.40% [f] | [g] | [g] | [g] | [g] | [g] | [g] | | | | | |
| Arthralgia | 2231 [a] | 96 [b] | 4.3% [a] | 3.5% [c] | 5.2% [c] | 702 [a] | 24 [b] | 3.4% [a] | 2.2% [c] | 5.0% [c] | | | | | | | | | | | | | | | | | 0.9% [d] | 0.81% [e] | -0.68% [f] | 2.48% [f] | [g] | [g] | [g] | [g] | [g] | [g] | | | | | |
| Myalgia | 2231 [a] | 56 [b] | 2.5% [a] | 1.9% [c] | 3.2% [c] | 702 [a] | 16 [b] | 2.3% [a] | 1.3% [c] | 3.7% [c] | | | | | | | | | | | | | | | | | 0.2% [d] | 0.66% [e] | -1.08% [f] | 1.48% [f] | 0.2 [h] | 0.1 [h] | 0.3 [h] | 0.250 [i] | 0.250 [j] | 0.250 [j] | 0.00010 [k] | -0.00064 [l] | -0.00054 [m] | 0.00064 [n] | 0.00074 [o] |
| Myopathy | | | | | | | | | | | | | | | | | | | | | | | | | | | 0.4% [p] | | 0.40% [p] | 0.40% [p] | 0.4 [q] | 0.2 [q] | 0.6 [q] | 0.250 [i] | 0.250 [j] | 0.250 [j] | 0.00040 [k] | -0.00020 [l] | 0.00020 [m] | 0.00020 [n] | 0.00060 [o] |
| Rhabdomyolysis (non-fatal) | | | | | | | | | | | | | 7,486 [r] | 4 [r] | 10% [s] | 1% [s] | 100% [s] | 0.0053433 | 0.0001456 [t] | 0.1368099 [u] | 55 [v] | 44 [v] | 66 [v] | 25.61 [w] | 17.05 [w] | 35.24 [w] | 13.68% [z] | | 0.25% [z] | 482.12% [z] | 1.0 [A] | 1.0 [j] | 1.0 [j] | 0.038 [A] | 0.038 [j] | 0.038 [j] | 0.00526 [k] | -0.00517 [l] | 0.00010 [m] | 0.18017 [n] | 0.18543 [o] |
| Rhabdomyolysis (fatal) | | | | | | | | | | | 9,815,000 [B] | | 3.0 [C] | 3,271,667 | 31 [B] | 10% [s] | 1% [s] | 100% [s] | 0.0000948 | 0.0000064 [t] | 0.0013449 [u] | 55 [v] | 44 [v] | 66 [v] | - | - | - | - | - | 1.0 [D] | 1.0 [j] | 1.0 [j] | - | - | - | 0.03322 [E] | -0.03227 [F] | 0.00095 [E] | 0.84403 [G] | 0.87725 [E] |
| **Total** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | **0.03898** [H] | -0.03269 [I] | **0.00629** [m] | 0.863044 [J] | **0.90203** [o] |

Sources and Notes

LB Lower bounds of the estimate
PE Point estimate
PY Person-Year
SE Standard error of the point estimate
QALY Quality-adjusted life-years
UB Upper bounds of the estimate
- Not applicable

[a] NDA 20-740/S019 (Ref S11), Labeling, PDF page 15, Table 5. Only the Adverse Events where the Baycol percentage is greater than the Placebo percentage are listed.
[b] =Number of Patients x Estimated Risk (i.e., =(B)x(D) or =(G)x(I)).
[c] Calculated using the Matlab Statistics Toolbox Binofit function (Ref S1).
[d] =(D)-(I). Assumes the risk per patient is independent of the treatment duration.
[e] =SQRT( (D)x(1-(D))/(B) + (I)x(1-(I))/(G) ) according to Eqn (2.13) in Fleiss (1981, Ref S2).
[f] =(AB)±1.96x(AC). See Eqn (7.6) in Fleiss (1981, Ref S2).
[g] Assumed to be negligible.
[h] Assumed to be equal to 1 - the QALY utility value while experiencing myalgia used by Erickson et al. (2013, Ref S15) Table 1 (0.80 (0.70,0.90)).
[i] Assumed value based on 'Patients who developed myalgias incurred a ... 3-month quality-of-life decrement due to the muscle pain' (Erickson et al., 2013, Ref S15, page 1251).
[j] Assumed equal to the point estimate.
[k] =(AB)x(AF)x(AI).
[l] =-SQRT( (((AD)-(AB))x(AF)x(AI))^2 + ((AB)x((AG)-(AF))x(AI))^2 + ((AB)x(AF)x((AJ)-(AI)))^2 ), based on the assumption that the uncertainties in the terms are uncorrelated.
[m] =(AL)+(AM).
[n] =SQRT( (((AE)-(AB))x(AF)x(AI))^2 + ((AB)x((AH)-(AF))x(AI))^2 + ((AB)x(AF)x((AK)-(AI)))^2 ), based on the assumption that the uncertainties in the terms are uncorrelated.
[o] =(AL)+(AO).
[p] NDA 20-740/S019 (Ref S11), Labeling, Warnings, PDF page 11.
[q] Assumed to be equal to 2 x the QALY disutility value while experiencing myalgia assumed by Erickson et al. (2013, Ref S15).
[r] Graham et al. (2004, Ref S14), Table 1 (Monotherapy).
[s] It is assumed that adverse events in the FDA Adverse Event Reporting System (AERS) are underreported. It is assumed that the AERS reporting rate is 10% (1% to 100%) based on a memo from Mackey to Raczkowski dated 2002-03-26 (NDA 21-107/S005, Ref S25, PDF page 464). The reporting rate assumed by Mackey is based on Rogers et al. (1988, Ref S5) and Scott et al. (1987, Ref S4). It is assumed that this underreporting rate was known to the FDA at the time of the market withdrawal (2001-08-08) because it was also reported in a memo from Graham (FDA) dated 1996-04-17 (NDA 16-832/S013, Ref S18, PDF pages 34-35). Staffa et al. (2002, Ref S13) indicated that the reporting rate may be as low as 1%.
[t] The 95% confidence intervals are based on the assumption that the number of events (O) are sampled from a Poisson distribution. The confidence intervals were calculated using the Matlab Statistics Toolbox Poissfit function (Ref S1). The lower bounds was then divided by the estimated number of person-years (N) and the upper bounds for the estimated adverse event reporting rate (R). Therefore the lower bounds for the 95% confidence interal is approximately ((O)-SQRT((O)))/((N)x(R)) for large (O). This may overestimate the uncertainty in the estimate.
[u] The 95% confidence intervals are based on the assumption that the number of events (O) are sampled from a Poisson distribution. The confidence intervals were calculated using the Matlab Statistics Toolbox Poissfit function (Ref S1). The upper bounds was then divided by the estimated number of person-years (N) and the lower bounds for the estimated adverse event reporting rate (Q). Therefore the upper bounds for the 95% confidence interal is approximately ((O)+SQRT((O)))/((N)x(Q)) for large (O). This may overestimate the uncertainty in the estimate.
[v] The average age of the Pravastatin patients in the Shepherd et al. (1995, Ref S7) study was 55.2 years with a 5.5 year standard deviation. It is assumed that the Baycol (Cerivastatin) and Pravastatin patients would have a similar age distribution. Rounded to the nearest integer value.
[w] Assumed equal to the life expectancy of the patient at the time the treatment began (i.e., (Y) ((Z),(AA)) ).
[x] The average age of the Pravastatin patients in the Shepherd et al. (1995, Ref S7) study was 55.2 years with a 5.5 year standard deviation. It is assumed that the Baycol (Cerivastatin) and Pravastatin patients would have a similar age distribution.
[y] Therefore the PE, LB, and UB values were based on the average life expectancy reported in Arias et al. (2008, Ref S3) Table 1 for the ages values rounded to 55, 66, and 44 years respectively.
[z] =Estimated Risk per Person-Year of Treatment (i.e., (S) ((T),(U)) ) x Years of Treatment ( (Y) ((Z),(AA)) ).
[A] Based on the assumption that the patient utility before treatment is 1, and the assumption in Erickson (2013, Ref S15) Table 1 footnote that 'Patients experience 0 QALYs for the 2 weeks of hospitalization with rhabdomyolysis.' This does not include the $55,794 estimated costs in 2010 US $.
[B] Staffa et al. (2002, Ref S13), Table 1.
[C] Estimated based on number of statin fills among adults and number of adults reported in Sarpong and Zuvekas (2014, Ref S16), Figures 1 and 2.
[D] Based on the assumption that the patient utility before treatment is 1. The utility value for death is 0 by definition.
[E] Assumed equal to the reduction in the Life expectancy in years relative to the baseline life expectancy in Arias et al. (2008, Ref S3) Table 1 if the annual probabiity of death due to Rhabdomyolysis between the time the treatment began ((V), ((W), (X))) and 109 years is ((S), ((T), (U))). This value is undiscounted and does not account for reduced life expectancy due to the indicated condition.
[F] =(AN)-(AL).
[G] =(AP)-(AL).
[H] =column total.
[I] =-SQRT(SUM((AM)^2)), based on the assumption that the uncertainties in the estimated risks for each adverse event are uncorrelated.
[J] =SQRT(SUM((AO)^2)), based on the assumption that the uncertainties in the estimated risks for each adverse event are uncorrelated.

Table S5. Estimated Risk of Baycol (cerivastatin sodium tablets, 0.2, 0.3, 0.4 and 0.8 mg) and other statins corresponding to the US market withdrawal of Baycol on 2001-08-08.

| (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) | (I) | (J) | (K) | (L) | (M) | (N) | (O) | (P) | (Q) | (R) | (S) | (T) | (U) | (V) | (W) | (X) | (Y) | (Z) | (AA) | (AB) | (AC) | (AD) | (AE) | (AF) | (AG) | (AH) | (AI) | (AJ) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Statin | Adverse Event (Rhabdomyolysis only) | Estimated Number of Prescriptions | Estimated Number of Prescriptions per PY | Estimated Number of Person-Years | Number of Reported Events | Estimated Adverse Event Reporting Rate | | | Estimated Risk per Person-Year of Treatment | | | | | Assumed Age to Begin Treatment (Years) | | | Assumed Treatment Duration (years) | | | Estimated Net Increase in Risk per Patient due to Statin | | | | | Assumed QALY Disuse Factor | | | Assumed Loss Duration (years) | | | Estimated Risk (QALY Lost per Statin Patient) | | | | |
| | | PE | PE | PE =(C)/(D) | | PE | LB | UB | PE =(F)/((E)x(G)) | LB-PE =(L)-(J) | LB | UB-PE =(N)-(J) | UB | PE | LB | UB | PE | LB | UB | PE =(J)x(R) | LB-PE | LB =(U)x(V) | UB-PE | UB =(U)x(X) | PE | LB | UB | PE | LB | UB | PE | LB-PE | LB | UB-PE | UB |
| Baycol (cerivastatin) | Rhabdomyolysis (non-fatal) | | | 7,486 [a] | 4 [a] | 10% [b] | 1% [b] | 100% [b] | 0.00534331 | -0.00519772 | 0.00014559 [c] | 0.13146658 | 0.13680989 [d] | 55 [e] | 44 [e] | 66 [e] | 25.61 [f] | 17.05 [f] | 35.24 [f] | 13.68% | -14.08% [g] | -0.39% | 336.7% [h] | 350.4% | 1.0 [i] | 1.0 [j] | 1.0 [j] | 0.038 [l] | 0.038 [j] | 0.038 [j] | 0.00526 [k] | -0.00541 [l] | -0.00015 [m] | 0.12951 [n] | 0.13477 [o] |
| | Rhabdomyolysis (fatal) | 9,815,000 [p] | 3.0 [q] | 3,271,667 | 31 [p] | 10% [b] | 1% [b] | 100% [b] | 0.00009475 | -0.00008831 | 0.00000644 [c] | 0.00125019 | 0.00134494 [d] | 55 [e] | 44 [e] | 66 [e] | - | - | - | - | - | - | - | - | 1.0 [r] | 1.0 [j] | 1.0 [j] | - | - | - | 0.03322 [s] | -0.03227 [t] | 0.00095 [s] | 0.84403 [u] | 0.87725 [s] |
| | **Total** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | **0.03848** [v] | -0.03272 [w] | **0.00576** [m] | 0.85391 [x] | **0.89239** [o] |
| Atorvastatin | Rhabdomyolysis (non-fatal) | | | 129,367 [a] | 7 [a] | 10% [b] | 1% [b] | 100% [b] | 0.00054110 | -0.00051935 | 0.00002175 [c] | 0.01060755 | 0.01114865 [d] | 55 [e] | 44 [e] | 66 [e] | 25.61 [f] | 17.05 [f] | 35.24 [f] | 1.39% | -1.41% [g] | -0.02% | 27.2% [h] | 28.6% | 1.0 [i] | 1.0 [j] | 1.0 [j] | 0.038 [l] | 0.038 [j] | 0.038 [j] | 0.00053 [k] | -0.00054 [l] | -0.00001 [m] | 0.01045 [n] | 0.01098 [o] |
| | Rhabdomyolysis (fatal) | 140,360,000 [p] | 3.0 [q] | 46,786,667 | 6 [p] | 10% [b] | 1% [b] | 100% [b] | 0.00000128 | -0.00000123 | 0.00000005 [c] | 0.00002663 | 0.00002791 [d] | 55 [e] | 44 [e] | 66 [e] | - | - | - | - | - | - | - | - | 1.0 [r] | 1.0 [j] | 1.0 [j] | - | - | - | 0.00045 [s] | -0.00038 [t] | 0.00007 [s] | 0.01808 [u] | 0.01853 [s] |
| | **Total** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | **0.00098** [v] | -0.00066 [w] | **0.00032** [m] | 0.02088 [x] | **0.02187** [o] |
| Fluvastatin | Rhabdomyolysis (non-fatal) | | | 3,292 [a] | 0 [a] | 10% [b] | 1% [b] | 100% [b] | 0.00000000 | 0.00000000 | 0.00000000 [c] | 0.11205588 | 0.11205588 [d] | 55 [e] | 44 [e] | 66 [e] | 25.61 [f] | 17.05 [f] | 35.24 [f] | 0.00% | 0.00% [g] | 0.00% | 287.0% [h] | 287.0% | 1.0 [i] | 1.0 [j] | 1.0 [j] | 0.038 [l] | 0.038 [j] | 0.038 [j] | 0.00000 [k] | 0.00000 [l] | 0.00000 [m] | 0.11038 [n] | 0.11038 [o] |
| | Rhabdomyolysis (fatal) | 37,392,000 [p] | 3.0 [q] | 12,464,000 | 0 [p] | 10% [b] | 1% [b] | 100% [b] | 0.00000000 | 0.00000000 | 0.00000000 [c] | 0.00002960 | 0.00002960 [d] | 55 [e] | 44 [e] | 66 [e] | - | - | - | - | - | - | - | - | 1.0 [r] | 1.0 [j] | 1.0 [j] | - | - | - | 0.00000 [s] | 0.00000 [t] | 0.00000 [s] | 0.01965 [u] | 0.01965 [s] |
| | **Total** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | **0.00000** [v] | 0.00000 [w] | **0.00000** [m] | 0.11211 [x] | **0.11211** [o] |
| Lovastatin | Rhabdomyolysis (non-fatal) | | | 775 [a] | 0 [a] | 10% [b] | 1% [b] | 100% [b] | 0.00000000 | 0.00000000 | 0.00000000 [c] | 0.47598445 | 0.47598445 [d] | 55 [e] | 44 [e] | 66 [e] | 25.61 [f] | 17.05 [f] | 35.24 [f] | 0.00% | 0.00% [g] | 0.00% | 1219% [h] | 1219% | 1.0 [i] | 1.0 [j] | 1.0 [j] | 0.038 [l] | 0.038 [j] | 0.038 [j] | 0.00000 [k] | 0.00000 [l] | 0.00000 [m] | 0.46884 [n] | 0.46884 [o] |
| | Rhabdomyolysis (fatal) | 99,197,000 [p] | 3.0 [q] | 33,065,667 | 19 [p] | 10% [b] | 1% [b] | 100% [b] | 0.00000575 | -0.00000540 | 0.00000035 [c] | 0.00008398 | 0.00008973 [d] | 55 [e] | 44 [e] | 66 [e] | - | - | - | - | - | - | - | - | 1.0 [r] | 1.0 [j] | 1.0 [j] | - | - | - | 0.00202 [s] | -0.00197 [t] | 0.00005 [s] | 0.05751 [u] | 0.05953 [s] |
| | **Total** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | **0.00202** [v] | -0.00197 [w] | **0.00005** [m] | 0.47236 [x] | **0.47437** [o] |
| Pravastatin | Rhabdomyolysis (non-fatal) | | | 33,149 [a] | 0 [a] | 10% [b] | 1% [b] | 100% [b] | 0.00000000 | 0.00000000 | 0.00000000 [c] | 0.01112818 | 0.01112818 [d] | 55 [e] | 44 [e] | 66 [e] | 25.61 [f] | 17.05 [f] | 35.24 [f] | 0.00% | 0.00% [g] | 0.00% | 28.5% [h] | 28.5% | 1.0 [i] | 1.0 [j] | 1.0 [j] | 0.038 [l] | 0.038 [j] | 0.038 [j] | 0.00000 [k] | 0.00000 [l] | 0.00000 [m] | 0.01096 [n] | 0.01096 [o] |
| | Rhabdomyolysis (fatal) | 81,364,000 [p] | 3.0 [q] | 27,121,333 | 3 [p] | 10% [b] | 1% [b] | 100% [b] | 0.00000111 | -0.00000109 | 0.00000002 [c] | 0.00003122 | 0.00003233 [d] | 55 [e] | 44 [e] | 66 [e] | - | - | - | - | - | - | - | - | 1.0 [r] | 1.0 [j] | 1.0 [j] | - | - | - | 0.00039 [s] | -0.00039 [t] | 0.00000 [s] | 0.02107 [u] | 0.02146 [s] |
| | **Total** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | **0.00039** [v] | -0.00039 [w] | **0.00000** [m] | 0.02375 [x] | **0.02414** [o] |
| Simvastatin | Rhabdomyolysis (non-fatal) | | | 40,940 [a] | 2 [a] | 10% [b] | 1% [b] | 100% [b] | 0.00048852 | -0.00048260 | 0.00000592 [c] | 0.01715849 | 0.01764701 [d] | 55 [e] | 44 [e] | 66 [e] | 25.61 [f] | 17.05 [f] | 35.24 [f] | 1.25% | -1.30% [g] | -0.05% | 43.9% [h] | 45.2% | 1.0 [i] | 1.0 [j] | 1.0 [j] | 0.038 [l] | 0.038 [j] | 0.038 [j] | 0.00048 [k] | -0.00050 [l] | -0.00002 [m] | 0.01690 [n] | 0.01738 [o] |
| | Rhabdomyolysis (fatal) | 116,145,000 [p] | 3.0 [q] | 38,715,000 | 14 [p] | 10% [b] | 1% [b] | 100% [b] | 0.00000362 | -0.00000342 | 0.00000020 [c] | 0.00005705 | 0.00006067 [d] | 55 [e] | 44 [e] | 66 [e] | - | - | - | - | - | - | - | - | 1.0 [r] | 1.0 [j] | 1.0 [j] | - | - | - | 0.00127 [s] | -0.00124 [t] | 0.00003 [s] | 0.03900 [u] | 0.04026 [s] |
| | **Total** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | **0.00175** [v] | -0.00134 [w] | **0.00041** [m] | 0.04250 [x] | **0.04425** [o] |

| Alternative Statin | Adverse Event (Rhabdomyolysis only) | Estimated Risk of Baycol compared to the Alternative Statin per Person-Year of Treatment | | | | | Assumed Age to Begin Treatment (Years) | | | Assumed Treatment Duration (years) | | | Estimated Net Increase in Risk per Patient due to Statin | | | | | Assumed QALY Disuse Factor | | | Assumed Loss Duration (years) | | | Estimated Risk of Baycol Compared to the Alternative Statin (QALY Lost per Statin Patient) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | PE =(F)/((E)x) | LB-PE | LB =(J)+(K) | UB-PE | UB =(J)+(M) | PE | LB | UB | PE | LB | UB | PE =(J)x(R) | LB-PE | LB =(U)x(V) | UB-PE | UB =(U)x(X) | PE | LB | UB | PE | LB | UB | PE | LB-PE | LB | UB-PE | UB |
| Atorvastatin | Rhabdomyolysis (non-fatal) | 0.00480221 | -0.01181256 [z] | -0.00701034 | 0.13146761 [A] | 0.13626982 | 55 [e] | 44 [e] | 66 [e] | 25.61 [f] | 17.05 [f] | 35.24 [f] | 12.30% | -30.53% [g] | -18.23% | 336.72% [h] | 349.02% | 1.0 [i] | 1.0 [j] | 1.0 [j] | 0.038 [l] | 0.038 [j] | 0.038 [j] | 0.00473 [k] | -0.01174 [l] | -0.00701 [m] | 0.12951 [n] | 0.13424 [o] |
| | Rhabdomyolysis (fatal) | 0.00009347 | -0.00009224 [z] | 0.00000123 | 0.00125019 [A] | 0.00134366 | 55 [e] | 44 [e] | 66 [e] | - | - | - | - | - | - | - | - | 1.0 [r] | 1.0 [j] | 1.0 [j] | - | - | - | 0.03277 [s] | -0.03259 [t] | 0.00018 [s] | 0.84366 [u] | 0.87643 [s] |
| | **Total** | | | | | | | | | | | | | | | | | | | | | | | 0.03750 [v] | -0.03464 [w] | 0.00286 [m] | 0.85354 [x] | 0.89104 [o] |
| Fluvastatin | Rhabdomyolysis (non-fatal) | 0.00534331 | -0.11217636 [z] | -0.10683306 | 0.13146658 [A] | 0.13680989 | 55 [e] | 44 [e] | 66 [e] | 25.61 [f] | 17.05 [f] | 35.24 [f] | 13.68% | -287.32% [g] | -273.64% | 336.73% [h] | 350.41% | 1.0 [i] | 1.0 [j] | 1.0 [j] | 0.038 [l] | 0.038 [j] | 0.038 [j] | 0.00526 [k] | -0.11051 [l] | -0.10524 [m] | 0.12951 [n] | 0.13477 [o] |
| | Rhabdomyolysis (fatal) | 0.00009475 | -0.00009314 [z] | 0.00000161 | 0.00125019 [A] | 0.00134494 | 55 [e] | 44 [e] | 66 [e] | - | - | - | - | - | - | - | - | 1.0 [r] | 1.0 [j] | 1.0 [j] | - | - | - | 0.03322 [s] | -0.03298 [t] | 0.00024 [s] | 0.84403 [u] | 0.87725 [s] |
| | **Total** | | | | | | | | | | | | | | | | | | | | | | | 0.03848 [v] | -0.11532 [w] | -0.07684 [m] | 0.85391 [x] | 0.89239 [o] |
| Lovastatin | Rhabdomyolysis (non-fatal) | 0.00534331 | -0.47601283 [z] | -0.47066952 | 0.13146658 [A] | 0.13680989 | 55 [e] | 44 [e] | 66 [e] | 25.61 [f] | 17.05 [f] | 35.24 [f] | 13.68% | -1219.1% [g] | -1205.4% | 336.73% [h] | 350.41% | 1.0 [i] | 1.0 [j] | 1.0 [j] | 0.038 [l] | 0.038 [j] | 0.038 [j] | 0.00526 [k] | -0.46888 [l] | -0.46361 [m] | 0.12951 [n] | 0.13477 [o] |
| | Rhabdomyolysis (fatal) | 0.00008901 | -0.00012187 [z] | -0.00003286 | 0.00125020 [A] | 0.00133921 | 55 [e] | 44 [e] | 66 [e] | - | - | - | - | - | - | - | - | 1.0 [r] | 1.0 [j] | 1.0 [j] | - | - | - | 0.03121 [s] | -0.03605 [t] | -0.00485 [s] | 0.84237 [u] | 0.87357 [s] |
| | **Total** | | | | | | | | | | | | | | | | | | | | | | | 0.03647 [v] | -0.47026 [w] | -0.43379 [m] | 0.85227 [x] | 0.88873 [o] |
| Pravastatin | Rhabdomyolysis (non-fatal) | 0.00534331 | -0.01228221 [z] | -0.00693890 | 0.13146658 [A] | 0.13680989 | 55 [e] | 44 [e] | 66 [e] | 25.61 [f] | 17.05 [f] | 35.24 [f] | 13.68% | -31.79% [g] | -18.10% | 336.73% [h] | 350.41% | 1.0 [i] | 1.0 [j] | 1.0 [j] | 0.038 [l] | 0.038 [j] | 0.038 [j] | 0.00526 [k] | -0.01223 [l] | -0.00696 [m] | 0.12951 [n] | 0.13477 [o] |
| | Rhabdomyolysis (fatal) | 0.00009365 | -0.00009367 [z] | -0.00000002 | 0.00125019 [A] | 0.00134383 | 55 [e] | 44 [e] | 66 [e] | - | - | - | - | - | - | - | - | 1.0 [r] | 1.0 [j] | 1.0 [j] | - | - | - | 0.03283 [s] | -0.03283 [t] | 0.00000 [s] | 0.84371 [u] | 0.87654 [s] |
| | **Total** | | | | | | | | | | | | | | | | | | | | | | | **0.03809** [v] | -0.03504 [w] | **0.00306** [m] | 0.85359 [x] | **0.89168** [o] |
| Simvastatin | Rhabdomyolysis (non-fatal) | 0.00485479 | -0.01792847 [z] | -0.01307368 | 0.13146747 [A] | 0.13632226 | 55 [e] | 44 [e] | 66 [e] | 25.61 [f] | 17.05 [f] | 35.24 [f] | 12.43% | -46.10% [g] | -33.67% | 336.72% [h] | 349.15% | 1.0 [i] | 1.0 [j] | 1.0 [j] | 0.038 [l] | 0.038 [j] | 0.038 [j] | 0.00478 [k] | -0.01773 [l] | -0.01295 [m] | 0.12951 [n] | 0.13429 [o] |
| | Rhabdomyolysis (fatal) | 0.00009114 | -0.00010514 [z] | -0.00001400 | 0.00125019 [A] | 0.00134133 | 55 [e] | 44 [e] | 66 [e] | - | - | - | - | - | - | - | - | 1.0 [r] | 1.0 [j] | 1.0 [j] | - | - | - | 0.03195 [s] | -0.03402 [t] | -0.00207 [s] | 0.84298 [u] | 0.87493 [s] |
| | **Total** | | | | | | | | | | | | | | | | | | | | | | | 0.03673 [v] | -0.03836 [w] | -0.00163 [m] | 0.85287 [x] | 0.88961 [o] |

Sources and Notes

LB Lower bounds of the estimate
PE Point estimate
PY Person-Year
QALY Quality-adjusted life-years
SE Standard error of the point estimate
UB Upper bounds of the estimate
- Not applicable

[a] Graham et al. (2004, Ref S14), Table 1 (Monotherapy).

[b] It is assumed that adverse events in the FDA Adverse Event Reporting System (AERS) are underreported. It is assumed that the AERS reporting rate is 10% (1% to 100%) based on a memo from Mackey to Raczkowski dated 2002-03-26 (NDA 21-107/S005, Ref S25, PDF page 464). The reporting rate assumed by Mackey is based on Rogers et al. (1988, Ref S5) and Scott et al. (1987, Ref S4). It is assumed that this underreporting rate was known to the FDA at the time of the market withdrawal (2001-08-08) because it was also reported in a memo from Graham (FDA) dated 1996-04-17 (NDA 16-832/S013, Ref S18, PDF pages 34-35). Staffa et al. (2002, Ref S13) indicated that the reporting rate may be as low as 1%.

[c] The 95% confidence intervals are based on the assumption that the number of events (F) are sampled from a Poisson distribution. The confidence intervals were calculated using the Matlab Statistics Toolbox Poissfit function (Ref S1). The lower bounds was then divided by the number of person-years (E) and the upper bounds for the estimated adverse event reporting rate (I). Therefore the lower bounds for the 95% confidence interal is approximately ((F)-SQRT((F)))/((E)x(I)) for large (F). This may overestimate the uncertainty in the estimate.

[d] The 95% confidence intervals are based on the assumption that the number of events (F) are sampled from a Poisson distribution. The confidence intervals were calculated using the Matlab Statistics Toolbox Poissfit function (Ref S1). The upper bounds was then divided by the number of person-years (E) and the lower bounds for the estimated adverse event reporting rate (H). Therefore the upper bounds for the 95% confidence interal is approximately ((F)+SQRT((F)))/((E)x(H)) for large (F). This may overestimate the uncertainty in the estimate.

[e] The average age of the Pravastatin patients in the Shepherd et al. (1995, Ref S7) study was 55.2 years with a 5.5 year standard deviation. It is assumed that the Baycol (Cerivastatin) and Pravastatin patients would have a similar age distribution. Rounded to the nearest integer value.

[f] Assumed equal to the life expectancy of the patient at the time the treatment began ( (R) ((S),(T)) ).
The average age of the Pravastatin patients in the Shepherd et al. (1995, Ref S7) study was 55.2 years with a 5.5 year standard deviation. It is assumed that the Baycol (Cerivastatin) and Pravastatin patients would have a similar age distribution.
Therefore the PE, LB, and UB values were based on the average life expectancy reported in Arias et al. (2008, Ref S3) Table 1 for the ages values rounded to 55, 66, and 44 years respectively.

[g] =-SQRT( ((K)x(R))^2 + ((J)x((S)-(R)))^2 )

[h] =SQRT(((M)*(U))^2+((J)*((T)-(R)))^2)

[i] Based on the assumption that the patient utility before treatment is 1, and the assumption in Erickson (2013, Ref S15) Table 1 footnote that 'Patients experience 0 QALYs for the 2 weeks of hospitalization with rhabdomyolysis.' This does not include the $55,794 estimated costs in 2010 US $.

[j] Assumed equal to the point estimate.

[k] =(U)x(Z)x(AC).

[l] =-SQRT( (((W)-(U))x(Z)x(AC))^2 + ((U)x((AA)-(Z))x(AC))^2 + ((U)x(Z)x((AD)-(AC)))^2 ), based on the assumption that the uncertainties in the terms are uncorrelated.

[m] =(AF)+(AG).

[n] =SQRT( (((Y)-(U))x(Z)x(AC))^2 + ((U)x((AB)-(Z))x(AC))^2 + ((U)x(Z)x((AE)-(AC)))^2 ), based on the assumption that the uncertainties in the terms are uncorrelated.

[o] =(AF)+(AI).

[p] Staffa et al. (2002, Ref S13), Table 1.

[q] Estimated based on number of statin fills among adults and number of adults reported in Sarpong and Zuvekas (2014, Ref S16), Figures 1 and 2.

[r] Based on the assumption that the patient utility before treatment is 1. The utility value for death is 0 by definition.

[s] Assumed equal to the reduction in the Life expectancy in years relative to the baseline life expectancy in Arias et al. (2008, Ref S3) Table 1 if the annual probabiity of death due to Rhabdomyolysis between the time the treatment began (e.g., (O) ((P),(Q)) ) and 109 years is ( (J) ((L),(N)) ). This value is undiscounted and does not account for reduced life expectancy due to the indicated condition.

[t] =(AH)-(AF).

[u] =(AJ)-(AF).

[v] =sum of the estimated non-fatal and fatal risks due to rhabdomyolysis.

[w] =-SQRT(SUM((AG)^2)), based on the assumption that the uncertainties in the estimated non-fatal and fatal risks due to rhabdomyolysis are uncorrelated.

[x] =SQRT(SUM((AI)^2)), based on the assumption that the uncertainties in the estimated non-fatal and fatal risks due to rhabdomyolysis are uncorrelated.

[y] =Baycol (AF) - alternative statin (AF).

[z] =-SQRT(Baycol (K)^2 + alternative statin (M)^2), based on the assumption that the uncertainty in the estimates are uncorrelated.

[A] =SQRT(Baycol (M)^2 + alternative statin (K)^2), based on the assumption that the uncertainty in the estimates are uncorrelated.

Table S6. Estimated Benefit of Baycol (cerivastatin sodium tablets, 0.2, 0.3, 0.4 and 0.8 mg) corresponding to the US market withdrawal on 2001-08-08.

Response in Patients with Primary Hypercholesterolemia, Mean Percent Change from Baseline after 8 Weeks

| (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) | (I) | (J) | (K) | (L) | (M) | (N) | (O) | (P) | (Q) | (R) | (S) | (T) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dosage | N | Total-C | | | LDL-C | | | HDL-C | | | Triglycerides | | | Relative Effect | | | Estimated Benefit (QALY Gained per Statin Patient) | | |
| | | Change | Net Change | Relative Effect | Change | Net Change | Relative Effect | Change | Net Change | Relative Effect | Change | Net Change | Relative Effect | | | | | | |
| | | PE | PE | PE | PE | PE | PE | PE | PE | PE | PE | PE | PE | PE =(H) | LB | UB | PE | LB | UB |
| Placebo | 608-620 [a] | 1% [a] | | | 0% [a] | | | 2% [a] | | | 0% [a] | | | | | | | | |
| Baycol, 0.2 mg once daily | 150-151 [a] | -18% [a] | -19.0% [b] | 0.95 [d] | -25% [a] | -25.0% [b] | 0.96 [d] | 9% [a] | 7.0% [b] | 0.98 [e] | -16% [a] | -16.0% [b] | 1.33 [f] | 0.96 [g] | 0.95 [h] | 0.98 [h] | 0.22289 [i] | 0.05627 [i] | 0.41172 [i] |
| Baycol, 0.3 mg once daily | 494-497 [a] | -22% [a] | -23.0% [b] | 1.15 [d] | -31% [a] | -31.0% [b] | 1.19 [d] | 8% [a] | 6.0% [b] | 0.99 [e] | -16% [a] | -16.0% [b] | 1.33 [f] | 1.19 [g] | 0.99 [h] | 1.19 [h] | 0.27638 [i] | 0.05867 [i] | 0.50025 [i] |
| Baycol, 0.4 mg once daily | 754-758 [a] | -24% [a] | -25.0% [b] | 1.25 [d] | -34% [a] | -34.0% [b] | 1.31 [d] | 7% [a] | 5.0% [b] | 1.00 [e] | -16% [a] | -16.0% [b] | 1.33 [f] | 1.31 [g] | 1.00 [h] | 1.31 [h] | 0.30312 [i] | 0.05923 [i] | 0.54866 [i] |
| Baycol, 0.8 mg once daily | 731-735 [a] | -30% [a] | -31.0% [b] | 1.55 [d] | -42% [a] | -42.0% [b] | 1.62 [d] | 9% [a] | 7.0% [b] | 0.98 [e] | -22% [a] | -22.0% [b] | 1.83 [f] | 1.62 [g] | 0.98 [h] | 1.62 [h] | 0.37445 [i] | 0.05812 [i] | 0.67775 [i] |
| Baycol, average | | | | | | | | | | | | | | 1.27 [j] | 0.98 [j] | 1.27 [j] | **0.29421** [j] | **0.05807** [j] | **0.53459** [j] |
| | | | | | | | | | | | | | | | | | | | |
| Pravastatin, 40 mg each evening | | | -20% [c] | 1.00 [d] | | -26% [c] | 1.00 [d] | | 5% [c] | 1.00 [e] | | -12% [c] | 1.00 [f] | 1.00 [g] | 1.00 [h] | 1.00 [h] | 0.23180 [k] | 0.05923 [k] | 0.41956 [k] |
| | | | | | | | | | | | | | | | | | | | |
| Baycol - Pravastatin | | | | | | | | | | | | | | 0.27 [l] | -0.02 [l] | 0.27 [l] | **0.06241** [l] | **-0.00116** [l] | **0.11503** [l] |

Sources and Notes

HDL-C High density lipoprotein cholesterol
LB Lower bounds of the estimate
LDL-C Low density lipoprotein cholesterol
PE Point estimate
QALY Quality-adjusted life-years
Total-C Total cholesterol
UB Upper bounds of the estimate

[a] NDA 20-740/S019 (Ref S11), Final Printed Labeling, PDF page 9, Table 1 (Intent-to-treat population).

[b] =Baycol Change-Placebo Change

[c] Results of the West of Scotland Coronary Prevention Study (WOSCOPS) reported in Shepherd et al. (1995, Ref S7) page 1304.

[d] =Net Change/Pravastatin Net Change, based on the statement in NDA 20-740/S019 (Ref S11, PDF page 6) that "Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C."

[e] =(1+Pravstatin Net Change)/(Net Change), based on the statement in NDA 20-740/S019 (Ref S11, PDF page 6) that "Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C."

[f] =Net Change/pravastatin Net Change. This value is for comparison purposes only.

[g] Assume that the LDL-C reduction (H) has the main effect on QALY benefit.

[h] Assume the lower and upper bounds for the relative effect are equal to the minimum and maximum values for (E), (H) and (K).

[i] =Relative Effect (i.e., (O) ((P),(Q)) ) x Estimated Benefit ( (R) ((S),(T)) ) for Pravastatin. This assumes that the QALY benefits vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C.

[j] =assumed equal to the average value for the 0.2, 0.3, 0.4, and 0.8 mg Baycol doses.

[k] From columns (AA), (AC) and (AE) of Table S2. Based on reductions in death from all cardiovacular causes and nonfatal myocardial infarction observed in WOSCOPS reported in Shepherd et al. (1995, Ref S7) Table 2.

Note that NDA 20-740/S019 (Ref S11), Final Printed Labeling, states on PDF page 6 that:

*"The effect of BAYCOL® on cardiovascular morbidity and mortality has not been determined."*

NDA 20-740 (Ref S9), Medical Reviews, Part 2, further states on PDF page 33 that:

*"The inclusion of broad summary statements addressing certain demonstrated clinical benefits of lipid lowering, of summary data from the LRC-CPPT using cholestyramine, and of references to the 4S and WOSCOPS trials and their results in the label for cerivastatin should be deleted Such information is not essential for the safe and effective use of the drug. Furthermore, the inclusion of this information implies effectiveness of cerivastatin not demonstrated in well-controlled trials using the drug. At this point in time, there is sufficient general knowledge as to the presumed benefits of cholesterol lowering such that no* ***explicit*** *rationale for treatment need be provided in labeling."*

It is however assumed the results of the WOSCOPS did provide some implicit rationale for the benefits in the FDA decision making even if these benefits were not explicitly indicated on the labeling.

[l] =Baycol estimate-pravastatin estimate. Note this difference is also assumed to apply to the lower and upper bounds because the uncertainties in the Baycol and pravastatin estimates are correlated.

### *Cylert (pemoline)*

This section describes the estimated risks and benefits of Cylert based on information in Refs S3 through S5, S17 through S22, and S25. The calculation steps and values are provided in Table S7 and Table S8 and the supporting sources and notes.

Cylert was originally approved in January 1975 for treatment of attention deficit-hyperactivity disorder (ADHD) (NDA 16-832, Ref S17). Because information concerning the original approval is not posted at the Drugs@FDA website, we instead estimated the risks and benefits corresponding to the original approval using an indirect approach based on post-marketing information c. 1996 (submitted by the manufacturer) in NDA 16-832/S013 (Ref S18) and /S014 (Ref S19), and the estimated risks and benefits of FDA approved alternative therapy (i.e., Ritalin). This information focused primarily on the risk of acute liver failure (ALF) associated with Cylert. There were 10 cases of ALF that had been reported as of 1996 involving children less than 19 years old that resulted in death or liver transplantation. Estimates of the benefits of treating ADHD with Cylert based on information reported in the National Institute of Mental Health Multimodal Treatment Study of Children With ADHD (MTA Study), a randomized, controlled study of 579 children designed to examine the intermediate and long-term effectiveness of treatment options for ADHD (Jensen 2005, Ref S21). In both the risk and benefit analyses, treatment duration (Tt) was assumed to be 14 months (Jensen 2005, Ref S21), while the quality of life lost and benefit duration (*Tq*) was assumed to be equal to life expectancy after the adverse event occurs or is prevented. The latter value was assumed be 66.1 years, the average life expectancy in the US for 5 to 19 year olds in 1999-2001 (Arias et al. 2008, Ref S3, Table 1).

It was further assumed that the annual risks and benefits of the treatment would remain constant over the patient's lifetime.

The risks and benefits corresponding to the original FDA approval were then estimated in terms of QALY lost and gained per patient based on these assumptions and information. The risk of acute liver failure associated with Cylert (when compared to non-medical treatment) was estimated to be 0.00897 (0.00257, 0.16107) QALY lost per patient based on the post-marketing information in NDA 16-832/S013 (Ref S18) and /S014 (Ref S19) (see Table S7). This estimate, which is based on information as of 1996, is most likely larger than the estimate for original FDA approval in 1975 because NDA 16-832/ S014 (Ref S19) also proposed the addition of a new black box warning for increased ALF risk. Therefore it was assumed that the estimated risk corresponding to the original approval was 1/4 the post-marketing estimate based on the following comparisons to Ritalin: (1) the Cylert sponsor (Abbot) estimated that the risk of ALF with Cylert was 4.0 (1.19 to 13.9) times greater than Ritalin; (2) the FDA indicated that Cylert had no "documented advantage" over other treatments (e.g., Ritalin); and (3) Ritalin was also an FDA approved drug. Therefore if the risk of a "hypothetically safer Cylert" was **0.00224 (0.00064, 0.04027)** QALY lost per patient (i.e., 1/4 the postmarking estimate), then the risks and benefits of this "hypothetically safer Cylert"[2] would be the same or comparable to Ritalin, which was an FDA approved drug. Therefore the "hypothetically safer Cylert" would also be acceptable. In contrast to the risks, the estimated benefit of Cylert compared to routine community care (i.e., no medical management) was substantially higher, at **2.40 (1.57, 3.23)**

[2] The "hypothetically safer Cylert" is not an actual NCE such as Cylert or Ritalin. It is used to describe a hypothetical NCE with an acceptable risk compared to the benefit. The distinction is made between "hypothetically safer Cylert" and Ritalin because there may be other differences between the two NCEs, such as risks of other adverse events, which are not considered in this indirect comparison. It is also assumed that the "hypothetically safer Cylert" has the same benefits as both Cylert and Ritalin.

QALY gained per patient. A wider range of estimated benefits were also determined for different comorbidity subgroups (see Table S8).

Cylert was eventually withdrawn from the US market in May 2005, based primarily on accumulating information about the relative risks and benefits of Cylert when compared to alternative therapies. The FDA notice for withdrawal (Ref S22) indicated that the primary reason for the withdrawal was that given the occurrence of at least one additional case of ALF (despite the black box warning) and the availability of multiple other drug treatments for ADHD (e.g., Ritalin), "the risk of liver failure with this drug outweighs the potential benefits" .

To quantify the estimate risk and benefit of Cylert relative to the other available drug treatments (e.g., Ritalin) at the time of withdrawal, the estimated risks and benefits of Cylert was compared to the "hypothetically safer Cylert". The incremental risk of Cylert compared to the "hypothetically safer Cylert is **0.00673 (0.00192, 0.12080)** more QALY lost per patient. There is no (i.e.., **0.0**) incremental benefit of Cylert compared to Ritatlin (or the "hypothetically safer Cylert") because the FDA indicated that Cylert had no "documented advantage" over other treatments such as Ritalin.

Table S7. Estimated Risk of Cylert (pemoline) in 5-19 year olds.

| (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) | (I) | (J) | (K) | (L) | (M) | (N) | (O) | (P) | (Q) | (R) | (S) | (T) | (U) | (V) | (W) | (X) | (Y) | (Z) | (AA) | (AB) | (AC) | (AD) | (AE) | (AF) | (AG) | (AH) | (AI) | (AJ) | (AK) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Adverse Event | Estimated Number of Patients | | | Estimated Treatment Duration | Estimated Number of Person-Years | | | Reported Number | Estimated AE Reporting Rate | | | Estimated Number of Adverse Events | | | Absolute Risk | | | | Background Risk | | | | | | Net Risk | | | Assumed QALY Disuse Factor | | | Ass. Loss Duration (years) | Estimated Risk (QALY Lost per Pemoline Patient) | | | | |
| | | | | | | | | | | | | | | | AE/ Person-Year | AE/Patient | | | AE/Person-Year | | | AE/Patient | | | AE/Patient | | | | | | | | | | | |
| | PE | LB | UB | PE | PE | LB | UB | of AE | PE | LB | UB | PE =(I)/(J) | LB | UB | PE =(M)/(F) | PE =(P)x(E) | LB =(N)/(D) | UB =(O)/(C) | PE | LB | UB | PE =(T)x(E) | LB =(U)x(E) | UB =(V)x(E) | PE =(Q)-(W) | LB =(R)-(Y) | UB =(S)-(X) | PE | LB | UB | PE | PE =(Z)x(AC) x(AF) | LB-PE | LB =(AG)+(AH) | UB-PE | UB =(AG)+(AJ) |
| Acute Liver Failure | n/a | 400,000 [b] | 800,000 [b] | 1.167 [c] | 460,800 [d] | n/a | n/a | 10 [d] | 10% [e] | 1% [e] | 100% [e] | 100 | 4.80 [f] | 1839.0 [g] | 0.0002170 [h] | 0.0002532 | 0.0000060 | 0.0045976 | 0.0000010 [d] | 0.0000005 [d] | 0.0000040 [d] | 0.0000012 | 0.0000006 | 0.0000047 | 0.0002520 | 0.0000013 | 0.0045970 | | | | | | | | | |
| - non-fatal requiring | n/a | 400,000 [b] | 800,000 [b] | 1.167 [c] | 460,800 [d] | n/a | n/a | 7 [i] | 10% [e] | 1% [e] | 100% [e] | 70 | 2.81 [f] | 1442.3 [g] | 0.0001519 | 0.0001772 | 0.0000035 | 0.0036057 | 0.0000005 [k] | 0.0000003 [k] | 0.0000020 [j] | 0.0000006 | 0.0000003 | 0.0000023 | 0.0001766 | 0.0000012 | 0.0036054 | 0.392 [l] | 0.349 [l] | 0.444 [l] | 66.1 [m] | 0.00458 | -0.00457 [o] | 0.00000 | 0.08882 [p] | 0.09339 |
| - fatal | n/a | 400,000 [b] | 800,000 [b] | 1.167 [c] | 460,800 [d] | n/a | n/a | 3 [j] | 10% [e] | 1% [e] | 100% [e] | 30 | 0.62 [f] | 876.7 [g] | 0.0000651 | 0.0000760 | 0.0000008 | 0.0021918 | 0.0000005 [k] | 0.0000003 [k] | 0.0000020 [j] | 0.0000006 | 0.0000003 | 0.0000023 | 0.0000754 | -0.0000016 | 0.0021915 | 0.883 [q] | 0.883 [n] | 0.883 [n] | 66.1 [m] | 0.00440 | -0.00449 [o] | -0.00009 | 0.12347 [p] | 0.12787 |
| Total | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | **0.00897** [r] | -0.00641 [s] | **0.00257** | 0.15210 [t] | **0.16107** |

| (AO) | (AG) | (AH) | (AI) | (AJ) | (AK) |
|---|---|---|---|---|---|
| Comparison | Scaling Factor | Estimated Risk (QALY Lost per Patient) | | | |
| | PE | PE | LB-PE | LB | UB-PE | UB |
| Hypothetical Cylert with the same ALF risk as Ritalin | 0.25 [u] | **0.00224** [v] | -0.00160 [v] | **0.00064** [v] | 0.03802 [v] | **0.04027** [v] |
| Cylert - Hypothetical Cylert with the same ALF risk as Ritalin | 0.75 [u] | **0.00673** [v] | -0.00481 [v] | **0.00192** [v] | 0.11407 [v] | **0.12080** [v] |

Sources and Notes

AE Adverse event
LB Lower bounds of the estimate
PE Point estimate
QALY Quality-adjusted life-years
UB Upper bounds of the estimate
n/a Not available (unknown)

[a] 5 through 19 year olds in the US.
[b] Memo from G. Burkhart (Neurophamacological Drug Products, HFD-120, FDA), 1996-10-11, p 5 (Ref S19, PDF page 24).
[c] assumed equal to 14 months/(12 months/year), from Jensen et al. (2005, Ref S21).
[d] Memo from G. Burkhart (Neurophamacological Drug Products, HFD-120, FDA), 1996-09-19, p 4 (Ref S19, PDF page 15). Also memo from G. Burkhart (FDA), 1996-10-11, p 22 (ibid., PDF page 22).
[e] It is assumed that adverse events in the FDA Adverse Event Reporting System are under reported. It is assumed that the AERS reporting rate is 10% (1% to 100%) based on 1) a memo from Graham (FDA) dated 1996-04-17 (Ref S18, PDF pages 34-35); 2) a memo from Greg Burkhart (FDA) dated 1996-10-11 (Ref S19 PDF pages 21-24); and 3) a memo from Mackey to Raczkowski dated 2002-03-26 (Ref S25, PDF page 464). The reporting rate assumed by Mackey is based on Rogers et al. (1988, Ref S5) and Scott et al. (1987, Ref S4).
[f] Calculated assuming the number of adverse events has a Poisson distribution using the MATLAB poissfit function (Ref S1). The lower bounds was calculated assuming the number of SAEs=(I)/(L).
[g] Calculated assuming the number of adverse events has a Poisson distribution using the MATLAB poissfit function (Ref S1). The upper bounds was calculated assuming the number of SAEs=(I)/(K).
[h] =1/4608. A memo from Greg Burkhart to Paul Leber, October 11, 1996, p 3. (Ref S19, PDF page 22) stated that 'If 10% of the actual cases have been reported to the FDA then the IR would be about 1 per 4,608 PYs of Cylert use.'
[i] There were 7 US cases reported to the FDA involving <19 year old patients with acute liver failure resulting in non-fatal liver transplant, from Memo from N. Chamberlin (Reports Evaluation Branch, HFD-735, FDA), April 12, 1996, p 5 (Ref S18, PDF page 24). The SRS case numbers are New '96, 1416420, 1414590, 678873/646579, 1566207, 1570348/1621962, and 386667/659770.
[j] There were 3 US cases reported to the FDA involving <19 year old patients with acute liver failure resulting in death, from Memo from N. Chamberlin (Reports Evaluation Branch, HFD-735, FDA), April 12, 1996, p 5 (Ref S18, PDF page 24). The SRS case numbers are 563032/569850, 329404/127938, and 'New '93'.
[k] Assumed that '50% of fulminant liver failure cases die before making it to transplant', from Memo from G. Burkhart (Neurophamacological Drug Products, HFD-120, FDA), 1996-09-19, p 4 (Ref S19, PDF page 15). Therefore 50% were fatal and 50% were non-fatal.
[l] The disutility due to non-fatal acute liver failure is assumed to be equal to 1 minus the EQ-5D utility score 12 months after transplant reported in Longworth (2003, Ref S20) Table 1 (i.e., =1-0.608).
[m] Average life expectancy in the US for 5 to 19 year olds, from Arias et al. (2008, Ref S3) Table 1.
[n] Assumed equal to the point estimate.
[o] =-SQRT( (((AA)-(Z))*(AC)*(AF))^2 + ((Z)*((AD)-(AC))*(AF))^2 ), based on the assumption that the uncertainty in these terms are uncorrelated.
[p] =-SQRT( (((AB)-(Z))*(AC)*(AF))^2 + ((Z)*((AE)-(AC))*(AF))^2 ), based on the assumption that the uncertainty in these terms are uncorrelated.
[q] The disutility due to death is assumed to be equal to the utility before treatment. The assumed value (0.883) for a 'health state' of '11211' is from Jensen et al. (2005, Ref S21).
[r] =column total.
[s] =-SQRT(SUM((AH)^2)), based on the assumption that the uncertainties in the estimated non-fatal and fatal risks due to rhabdomyolysis are uncorrelated.
[t] =SQRT(SUM((AJ)^2)), based on the assumption that the uncertainties in the estimated non-fatal and fatal risks due to rhabdomyolysis are uncorrelated.
[u] The risks of 'Cylert with the same ALF risk as Ritalin' are assumed to be 1/4 the risks of Cylert, based on estimated relative risk of acute liver failure reported in NDA 16-832/S014 (Ref S19), PDF page 27.
[v] Cylert estimate x (AO)

Table S8. Estimated Benefits of Cylert (pemoline).

| (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) | (I) | (J) | (K) | (L) | (M) | (N) | (O) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Comorbidity Subgroup | Sample Size | | Normalization Rate | | | | EQ-5D Utility Weight | | | Benefit Duration (years) | Incremental Benefit (EQ-5D QALY Gained) | | | |
| | Routine Community Care | Medical Management | Routine Community Care | Medical Management | Increase due to Medical Management | | Before Treatment (Health state 11211) | After Treatment (Health state 11111) | Increase due to Treatment | | | | | |
| | | | PE | PE | PE =(E)-(D) | SE | PE | PE | PE =(I)-(H) | PE | PE =(F)x(J)x(K) | SE =(G)x(J)x(K) | LB =(L)-1.96x(M) | UB =(L)+1.96x(M) |
| Children with ADHD only | 42 [a] | 46 [a] | 31% [b] | 57% [b] | 26% | 10.2% [c] | 0.883 [d] | 1.000 [d] | 0.117 | 66.08 [e] | 2.01 | 0.79 | 0.46 | 3.56 |
| Children with ADHD plus internalizing disorder | 19 [a] | 20 [a] | 21% [b] | 80% [b] | 59% | 12.9% [c] | 0.883 [d] | 1.000 [d] | 0.117 | 66.08 [e] | 4.56 | 1.00 | 2.60 | 6.52 |
| Children with ADHD plus externalizing disorder | 54 [a] | 40 [a] | 28% [b] | 58% [b] | 30% | 9.9% [c] | 0.883 [d] | 1.000 [d] | 0.117 | 66.08 [e] | 2.32 | 0.77 | 0.82 | 3.82 |
| Children with ADHD plus both types of disorder | 31 [a] | 38 [a] | 16% [b] | 39% [b] | 23% | 10.3% [c] | 0.883 [d] | 1.000 [d] | 0.117 | 66.08 [e] | 1.78 | 0.80 | 0.22 | 3.34 |
| All children with ADHD | 146 [a] | 144 [a] | 25% [b] | 56% [b] | 31% | 5.5% [c] | 0.883 [d] | 1.000 [d] | 0.117 | 66.08 [e] | **2.40** | 0.42 | **1.57** | **3.23** |
| Minimum | | | | | | | | | | | 1.78 | 0.42 | 0.22 | 3.23 |
| Maximum | | | | | | | | | | | 4.56 | 1.00 | 2.60 | 6.52 |

Sources and Notes

PE Point estimate

[a] 'Normalization Rate' from Jensen et al. (2005, Ref S21) Table 1.

[b] 'Normalization Rate' from Jensen et al. (2005, Ref S21) Table 1.

[c] =sqrt( (D)x(1-(D))/(B) + (E)x(1-(E))/(C) ) according to Eqn (2.13) in Fleiss (1981, Ref S2)

[d] EQ-5D Utility weight from Jensen et al. (2005, Ref S21) Table 1.

[e] The average life expectancy in the US for 5 to 19 year olds in 1999-2001. Calculated value from Arias et al. (2008, Ref S3) Table 1.

### *Lotronex (alosetron hydrochloride)*

This section describes the estimated risks and benefits of Lotronex based on information in Refs S3 through S5, S18, and S23 through S29. The calculation steps and values are provided in Table S9 through Table S18 and the supporting sources and notes.

Lotronex was originally approved in February 2000 for the treatment of irritable bowel syndrome (IBS) in women whose predominant bowel symptom is diarrhea (NDA 21-107, Refs S23 and S24, Final Printed Labeling, PDF page 8). The estimated risk of Lotronex at the time of approval was quantified based on the risk of acute ischemic colitis reported in the warnings section of the FDA approved labeling, assuming that the quality of life disutility and loss duration were 0.019 (0.014 to 0.41) life units and 7 (50 to 15) days lost based on QALY information reported by Ladabaum et al (2003, Ref S26). The resulting estimated risk of Lotronex was **0.0000026 (0.0000003, 0.0000188)** QALY lost per patient (see Table S9).

The estimated benefit of Lotronex at the time of approval was quantified based on the quality of life results from two clinical trials (S3BA3001 and S3BA3002) reported in the NDA (NDA 21-107/S005, Ref S25, PDF pages 457-462). These results were based on patient responses to four social scale and four work scale questions in an Irritable Bowel Syndrome Quality of Life (IBSQoL) questionnaire. The social and work scale utility gained was assumed to be equal to the percentage of all Lotronex recipients who were “always” or “often” affected by IBS and were “seldom” or “never” affected during the last month of the 3-month trial. It was stated in the approval documentation that this utility metric “could be regarded as the true anticipated benefit to be weighed against a risk of severe injury.” (NDA 21-107/S005, Ref S25, PDF page 459).The

overall quality of life utility was assumed to be the average of the utility results for the four social scale and four work scale problems or symptoms. The duration of the benefit (*Tq*) was assumed to be 0.25 years corresponding to the length of the study. The resulting estimated benefit of Lotronex was **0.02625 (0.01346, 0.03904)** QALY gained per patient (see Table S10).

Lotronex was voluntarily withdrawn from the US market in November 2000 (approximately 9 months after initial approval) after an FDA reassessment determined that the "overall risk-benefit could not justify continued market availability from a public health perspective without implementation of restricted distribution" (NDA-21-107/S005, Ref S25, PDF pages 27-28). This reassessment was based on post-marketing reports of serious complications (hospitalization, surgery, or death) resulting from severe constipation and ischemic colitis-related AEs.

Revised estimates of risk and benefit at the time of market withdrawal were recalculated based on information that was assumed to be available at that time. The estimated risk of Lotronex was based primarily on information disclosed in an internal FDA review memorandum (Uhl et al. (FDA) to Talarico (FDA) dated 2000-11-16 on PDF pages 684-706 of ibid), which provided information on the number of events resulting in hospitalization, surgery, or death reported as of November 10, 2000, and corresponding estimates of the number of prescriptions filled; this estimate includes three deaths that were "probably associated" with Lotronex (PDF page 59 of NDA 21-107/S005 (Ref S25)). It was further assumed that AEs in the FDA Adverse Event Reporting System (AERS) were underreported by a factor of 10% (1% to 100%) (Rogers et al. (1998, Ref S5); Scott et al. (1987, Ref S4); PDF page 464 of NDA 21-107/S005). The quality of life disutility and loss duration (*Tq*) values for the reported SAEs were assumed to be the same as used by Ladabaum (2003, Ref S26). One exception was the assumed QALY lost duration for SAEs resulting in death, which were assumed to be the undiscounted life expectancy at the time

of death. This value was assumed be 32.85 years, which is the weighted average life expectancy for 18 through 109 year old US females in 1999-2001 from Arias et al. (2008, Ref S3, Table 3). The resulting estimated risk of Lotronex corresponding to the market withdrawal was **0.0024260 (0.0006434, 0.0741119)** QALY lost per patient (Table S11).

The FDA subsequently reinstated the approval and marketing of Lotronex in June 2002 with more restrictive labeling (NDA 21-107/S005, Ref S25), which narrowed the originally approved indication to use of the drug in a population for whom the benefits of the drug may outweigh the risks, namely for women with severe diarrhea-predominant IBS who (1) have chronic IBS symptoms (generally lasting 6 months or longer); (2) have anatomic or biochemical abnormalities of the gastrointestinal tract excluded; , and (3) failed to respond to conventional therapy. Estimates of the risks and benefits of Lotronex were recalculated based on QALY data assumed to be available in June 2002.

Three pairs of risk and benefit estimates corresponding to the 2002 FDA decision were determined based on three different approaches. The first approach used a simplified model similar to that used for the other drugs. The other approaches used more detailed decision analysis and relative value-adjusted life-years (RVALYs) models reported by Ladabaum (2003, Ref S26) and Lynd et al. (2010, Ref S27), respectively.

The estimated risk of Lotronex using the simplified model was quantified based information on the number of reported SAEs of severe constipation or ischemic colitis, and corresponding estimates of the number of patients reported in the approval documentation (NDA 21-107/S005, Ref S25, e.g., PDF page 59); this included five deaths that were “possibly” drug-associated. It was further assumed that 16.9% of the SAEs could be attributed to background (NDA 21-

107/S005, Ref S25, PDF page 82). The quality of life disutility and loss duration values were assumed to be the same as used the in the original risk estimate. The resulting estimated risk of Lotronex corresponding to re-approval was **0.0033521 (0.0000510, 0.0781041)** QALY lost per patient (see Table S12).

The estimated benefit of Lotronex at the time of re-approval was updated to include the lost activity and productivity results from an "Urgency Study" (Study S3B40031; NDA 21-107/S005 (Ref S25, PDF pages 171 and 173). The lost activity and productivity utility gained was assumed to be equal the reduction in the time lost for patients treated with Lotronex when compared to placebo, which was then normalized by the total number of hours possible. The overall quality of life utility was assumed to be the average of the utility results for the lost activity and productivity metrics, in addition to the previous results from the four social scale and four work scale problems or symptoms from the original S3BA3001 and S3BA3002 trials utilized for initial approval (NDA 21-107/S005, Ref S25, PDF pages 457-462). The duration of the benefit (*Tq*) was assumed to be 0.25 years corresponding to the length of the study. The resulting estimated benefit of Lotronex was **0.01590 (0.00710, 0.02469)** QALY gained per patient (see Table S13).

The risks and benefits of Lotronex were also estimated using the decision analytical model reported by Ladabaum (2003, Ref S26). This model assumed a 6-month treatment in two phases, the first lasting one month and, the second lasting 5 months; the second phase was initiated only for patients who were considered to have had an adequate response to the first phase. Although the risk and benefit results reported by Ladabaum were successfully duplicated (see Table S14 and Table S15), these results are not considered to be directly applicable to the current analysis since (1) it was assumed that 28% of the Lotronex patients would receive "adequate relief" with

standard care, which is different than quoted in the FDA-approved labeling; and (2) the life expectancy for QALY lost was discounted. Therefore, several parameters in the Ladabaum model were revised, including (1) none of the Latronex patients would have adequate relief (since the box warning in the label states that the drug is indicated only for women with severe diarrhea-predominant IBS who have failed to respond to conventional therapy (NDA 21-107/S005, Ref S25, PDF page 10); and (2) life expectancy was not discounted because the current analysis is not intended to compare benefits to discounted costs. Following these modifications, the resulting risk and benefit estimates using the decision analytical model were **0.001030 (0.000549, 0.001579)** QALY lost and **0.004604 (0.004140, 0.008560)** QALY gained per patient who begins treatment (see Table S16 and Table S17). These results are approximately 30% of the estimates calculated in our "simplified" model (see Table S12 and Table S13). These differences are partially attributed to the assumption that only 42% of the patients have adequate relief with Lotronex and continue treatment after the first month. Other sources for differences include (1) different probabilities of AEs based on different interpretation of the SAE risks reported in NDA 21-107/S005 (Ref S25), and different methods and data used to estimate the quality of life benefits. However, the resulting risk/benefit ratios using the two methods yield similar values (i.e., 0.22 versus 0.21).

The risks and benefits of Lotronex can also be estimated from results of the “discrete event simulation model” reported in Lynd *et al* (2010, Ref S27), who found that the incremental risk and benefit of Lotronex compared to a placebo was 0.0008 (0.0005, 0.0011) and 0.0312 (0.0167, 0.0462) relative value-adjusted life-years (RVALYs) per patient for a 52 week treatment, for all simulated Lotronex patients with mild, moderate, and severe symptoms at baseline. Therefore, the mean incremental net benefit for all simulated patients was 0.0304 (0.0159, 0.0454)

RVALYs per patient. However, and as indicated in the FDA-approved labeling, Lotronex was reapproved only for patients with severe symptoms, for whom Lynd *et al* also reported that the incremental net benefit was 0.03598 (0.02349, 0.04877) RVALYs per patient. Assuming that the incremental risk does not depend on the severity of baseline symptoms (as indicated in Figure 3 of Lynd *et al*), then the estimated incremental risks and benefits for patients with severe baseline symptoms are **0.0008 (0.0005, 0.0011)** and **0.03678 (0.02414, 0.04942)**. RVALYs per patient for a 52 week treatment (see Table S18).

Table S9. Estimated Risk of Lotronex (alosetron) corresponding to the FDA decision to approve NDA 21-107 on 2000-02-11 (Based on Serious Adverse Events observed in Clinical Trials).

| (A) | (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) | (I) | (J) | (K) | (L) | (M) | (N) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Serious Adverse Event (SAE) | Estimated Risk per Patient | | | Assumed QALY Disutility | | | Assumed Loss Duration (Years) | | | Estimated Risk (QALY Lost per Alosetron Patient) | | | | |
| | PE | LB | UB | PE | LB | UB | PE | LB | UB | PE =(A)x(D)x(G) | LB-PE | LB =(J)+(K) | UB-PE | UB =(J)+(M) |
| Ischemic colitis (reported cases resolved over several days to weeks without sequelae or complications following supportive management) | 0.001429 [b] | 0.001000 [a,b] | 0.010000 [a,b] | 0.0960 [c] | 0.0207 [c] | 0.1525 [c] | 0.019 [d] | 0.014 [d] | 0.041 [d] | 0.0000026 | -0.0000023 [e] | 0.0000003 | 0.0000161 [f] | 0.0000188 |
| **Total** | | | | | | | | | | **0.0000026** [g] | -0.0000023 [g] | **0.0000003** | 0.0000161 [g] | **0.0000188** |

Sources and notes:

IC Ischemic colitis
LB Lower bounds of the estimate
PE Point estimate
QALY Quality-adjusted life-years
SAE Serious adverse event
SCSC Serious complication of severe constipation
UB Upper bounds of the estimate

[a] NDA 21-107 (Ref S24), Final Printed Labeling, Warnings, pages 7-8. (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21107a_Lotronex_prntlbl_P1.pdf, PDF pages 8-9)

[b] NDA 21-107/S005 (Ref S25), PDF pages 33 and 55.

[c] The disutility for out-patient complications is assumed to be 1/2 the disutility for hospitalization, based on Ladabaum (2003, Ref S26) page 1024. The disutility for hospitalization is assumed to be equal to the utility of active irritable bowel syndrome (0.6740 (0.6413 to 0.7049) ) minus the utility of hospitalization (0.482 (0.4 to 0.6) ), based on Ladabaum Table 1.

[d] The disutility for out-patient complications is assumed to be equal to 7 (5 to 15) days, based on Ladabaum (2003, Ref S26) Table 1.

[e] =-SQRT( (((B)-(A))x(D)x(G))^2 + ((A)x((E)-(D))x(G))^2 + ((A)x(D)x((H)-(G)))^2 ), based on the assumption that the uncertainties in the terms are uncorrelated.

[f] =-SQRT( (((C)-(A))x(D)x(G))^2 + ((A)x((F)-(D))x(G))^2 + ((A)x(D)x((I)-(G)))^2 ), based on the assumption that the uncertainties in the terms are uncorrelated.

[g] Column total.

Table S10. Estimated Benefit of Lotronex (alosetron) corresponding to the FDA decision to approve NDA 21-107 on 2000-02-11 (Based on the results of 2 Clinical Trials).

| (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) |
|---|---|---|---|---|---|---|---|
| Study | N | Quality of Life Metric | Relative Benefit (utility) | Benefit Duration (years) | Estimated Benefit (QALY Gained per 12 Week Treatment) | | |
| | | | PE | PE | PE =(D)x(E) | LB | UB |
| S3BA3001 and S3BA3002 trials with diarrhea-predominant IBS | n/a | Social scale: Uncomfort | 0.19 [a] | 0.25 [d] | 0.04750 | n/a | n/a |
| | | Social scale: Avoid | 0.15 [a,b] | 0.25 [d] | 0.03750 | n/a | n/a |
| | | Social scale: Embarrass | 0.18 [a] | 0.25 [d] | 0.04500 | n/a | n/a |
| | | Social scale: In Way | 0.11 [a] | 0.25 [d] | 0.02750 | n/a | n/a |
| | | Work scale: Affected Success | 0.04 [c] | 0.25 [d] | 0.01000 | n/a | n/a |
| | | Work scale: Less work Done | 0.05 [c] | 0.25 [d] | 0.01250 | n/a | n/a |
| | | Work scale: Avoided Work | 0.06 [c] | 0.25 [d] | 0.01500 | n/a | n/a |
| | | Work scale: Not Done Well | 0.06 [c] | 0.25 [d] | 0.01500 | n/a | n/a |
| Minimum | | | | | 0.01000 | n/a | n/a |
| Average Benefit | | | | | **0.02625** [e] | **0.01346** [f] | **0.03904** [f] |
| Maximum | | | | | 0.04750 | n/a | n/a |

Sources and Notes

LB Lower bounds of the estimate
PE Point estimate
QALY Quality-adjusted life-years
UB Upper bounds of the estimate
n/a Indicates the value is not available and therefore unknown.

[a] 100% minus the digitized 'Joint' value from NDA 21-107/S005 (Ref S25), PDF page 462, Figure 7. This digitized value indicates the 'anticipated benefit to be weighted against a risk of severe injury' according to the description on PDF page 459 of ibid.

[b] 100% minus the numeric value for Figure 7 reported on PDF page 459 of NDA 21-107/S005 (Ref S25).

[c] 100% minus the digitized 'Joint' value from Ref S25, PDF page 462, Figure 8. This digitized value indicates the 'anticipated benefit to be weighted against a risk of severe injury' according to the description on PDF page 459 of ibid.

[d] NDA 21-107/S005 (Ref S25), PDF page 459.

[e] Column average.

[f] 95% confidence interval for the column (F) average assuming that the values are normally distributed.

Table S11. Estimated Risk of Lotronex (alosetron) corresponding to the US market withdrawal on 2000-11-20 (Based on Serious Adverse Events observed in Postmarketing Data).

| (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) | (I) | (J) | (L) | (M) | (N) | (O) | (P) | (Q) | (R) | (S) | (T) | (U) | (V) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Serious Adverse Event (SAE) | Estimted Number of Patients | Estimated Number of Prescriptions | Reported Number of SAE | Estimated Adverse Event Reporting Rate | | | Estimated Risk per Patient | | | Assumed QALY Disutility | | | Assumed Loss Duration (Years) | | | Estimated Risk (QALY Lost per Alosetron Patient) | | | | |
| | PE | PE | | PE | LB | UB | PE =(D)/((B)x(E)) | LB | UB | PE | LB | UB | PE | LB | UB | PE =(H)x(L)x(O) | LB-PE | LB =(R)+(S) | UB-PE | UB =(R)+(U) |
| IC not resulting in hospitalization, surgery or death | 275,000 [a] | 450,000 [b] | 19 [c] | 10% [e] | 1% [e] | 100% [e] | 0.000691 | 0.000042 [f] | 0.010789 [g] | 0.0960 [h] | 0.0207 [h] | 0.1525 [h] | 0.019 [i] | 0.014 [i] | 0.041 [i] | 0.0000013 | -0.0000016 [k] | -0.0000003 | 0.0000187 [l] | 0.0000199 |
| IC resulting in hospitalization without surgery or death | 275,000 [a] | 450,000 [b] | 25 [c] | 10% [e] | 1% [e] | 100% [e] | 0.000909 | 0.000059 [f] | 0.013420 [g] | 0.1920 [j] | 0.0413 [j] | 0.3049 [j] | 0.023 [m] | 0.015 [m] | 0.040 [m] | 0.0000041 | -0.0000052 [k] | -0.0000011 | 0.0000560 [l] | 0.0000601 |
| IC resulting in surgery but not death | 275,000 [a] | 450,000 [b] | 3 [c] | 10% [e] | 1% [e] | 100% [e] | 0.000109 | 0.000002 [f] | 0.003188 [g] | 0.1920 [j] | 0.0413 [j] | 0.3049 [j] | 0.064 [n] | 0.047 [n] | 0.120 [n] | 0.0000013 | -0.0000017 [k] | -0.0000004 | 0.0000381 [l] | 0.0000394 |
| IC resulting in surgery and death (probable association) | 275,000 [a] | 450,000 [b] | 2 [c] | 10% [e] | 1% [e] | 100% [e] | 0.000073 | 0.000001 [f] | 0.002627 [g] | 0.6740 [o] | 0.6413 [o] | 0.7049 [o] | 32.850 [p] | 32.850 [q] | 32.850 [q] | 0.0016102 | -0.0015900 [k] | 0.0000202 | 0.0565534 [l] | 0.0581636 |
| Severe constipation not resulting in hospitalization, surgery or death | 275,000 [a] | 450,000 [b] | 7 [d] | 10% [e] | 1% [e] | 100% [e] | 0.000255 | 0.000010 [f] | 0.005245 [g] | 0.0960 [h] | 0.0207 [h] | 0.1525 [h] | 0.019 [i] | 0.014 [i] | 0.041 [i] | 0.0000005 | -0.0000006 [k] | -0.0000001 | 0.0000092 [l] | 0.0000097 |
| Severe constipation resulting in hospitalization without surgery or death | 275,000 [a] | 450,000 [b] | 8 [d] | 10% [e] | 1% [e] | 100% [e] | 0.000291 | 0.000013 [f] | 0.005732 [g] | 0.1920 [j] | 0.0413 [j] | 0.3049 [j] | 0.023 [m] | 0.015 [m] | 0.040 [m] | 0.0000013 | -0.0000017 [k] | -0.0000004 | 0.0000243 [l] | 0.0000256 |
| Severe constipation resulting in surgery but not death | 275,000 [a] | 450,000 [b] | 5 [d] | 10% [e] | 1% [e] | 100% [e] | 0.000182 | 0.000006 [f] | 0.004243 [g] | 0.1920 [j] | 0.0413 [j] | 0.3049 [j] | 0.064 [n] | 0.047 [n] | 0.120 [n] | 0.0000022 | -0.0000029 [k] | -0.0000006 | 0.0000502 [l] | 0.0000525 |
| Severe constipation resulting in death (probable association) | 275,000 [a] | 450,000 [b] | 1 [d] | 10% [e] | 1% [e] | 100% [e] | 0.000036 | 0.000000 [f] | 0.002026 [g] | 0.6740 [o] | 0.6413 [o] | 0.7049 [o] | 32.850 [p] | 32.850 [q] | 32.850 [q] | 0.0008051 | -0.0008061 [k] | -0.0000009 | 0.0440519 [l] | 0.0448570 |
| Severe constipation resulting in death (possible association) | 275,000 [a] | 450,000 [b] | 0 | 10% [e] | 1% [e] | 100% [e] | 0.000000 | 0.000000 | 0.000000 | 0.6740 [o] | 0.6413 [o] | 0.7049 [o] | 32.850 [p] | 32.850 [q] | 32.850 [q] | 0.0000000 | 0.0000000 [k] | 0.0000000 | 0.0000000 [l] | 0.0000000 |
| **Total** | | | | | | | | | | | | | | | | **0.0024260** [r] | -0.0017827 [s] | **0.0006434** | 0.0716859 [t] | **0.0741119** |
| - Non-fatal | | | | | | | | | | | | | | | | 0.0000107 | -0.0000066 | 0.0000041 | 0.0000902 | 0.0001009 |
| - Fatal | | | | | | | | | | | | | | | | 0.0024153 | -0.0017827 | 0.0006327 | 0.0716858 | 0.0741011 |

Sources and notes:

AERS FDA Adverse Event Reporting System
IC Ischemit colitis
LB Lower bounds of the estimate
PE Point estimate
QALY Quality-adjusted life-years
SAE Serious adverse event
UB Upper bounds of the estimate

[a] NDA 21-107/S005 (Ref S25), PDF page 59, Table 4. The 275,000 patient estimate may based on an estimated 435,000 prescriptions 'dispensed between March and October 2000', based on information as of 2000-10-25 (ibid., PDF page 686). Estimates after market withdrawal indicate that '300,000 patients filled over 450,000 prescriptions' (ibid., PDF page 403).'

[b] Memo from Uhl et al. (FDA) to Talarico dated 2000-11-16 (NDA 21-107/S005, Ref S25, PDF page 686) indicates that there were 435,000 Lotronex prescriptions dispensed between March and October 2000. This information was provided to the HFD-180 Division of the FDA by GlaxoWellcome on October 25, 2000.

[c] Memo from Uhl et al. (FDA) to Talarico dated 2000-11-16 (NDA 21-107/S005, Ref S25, e.g. PDF page 686) indicates that as of 2000-11-10 there were 49 cases of ischemic colitis. Of these 49 IC cases, 30 cases required hospitalization. Of the 30 IC cases requiring hospitalization, 5 cases required surgery for an obstructed, necrotic, or ruptured bowel. Of the 5 IC cases requiring surgery, 2 cases resulted in death that was 'probably' associated with Lotronex.

[d] Memo from Uhl et al. (FDA) to Talarico dated 2000-11-16 (NDA 21-107/S005, Ref S25, e.g. PDF page 686) indicates that as of 2000-11-10 there were 21 cases of severe constipation. Of these 21 severe constipation cases, 14 cases required hospitalization. Of the 14 severe constipation cases requiring hospitalization, 5 cases required surgery for an obstructed, necrotic, or ruptured bowel and 1 case resulted in death that was 'probably' associated with Lotronex. The case that resulted in a death (#43) did not have surgury.

[e] It is assumed that adverse events in the FDA Adverse Event Reporting System (AERS) are underreported. It is assumed that the AERS reporting rate is 10% (1% to 100%) based on a memo from Mackey to Raczkowski dated 2002-03-26 (NDA 21-107/S005, Ref S25, PDF page 464). The reporting rate assumed by Mackey is based on Rogers et al. (1988, Ref S5) and Scott et al. (1987, Ref S4). It is assumed that this underreporting rate was known to the FDA at the time of the market withdrawal (2000-11-28) because it was also reported in a memo from Graham (FDA) dated 1996-04-17 (NDA 16-832/S013, Ref S18, PDF pages 34-35).

[f] Calculated assuming that the probabity of a reported SAE per patient has a Binomial distribution using the MATLAB binofit((D),(B)) function (Ref S1). The lower bounds was calculated by dividing the lower bounds for the binofit((D),(B)) probability estimate by (G).

[g] Calculated assuming that the probabity of a reported SAE per patient has a Binomial distribution using the MATLAB binofit((D),(B)) function (Ref S1). The upper bounds was calculated by dividing the upper bounds for the binofit((D),(B)) probability estimate by (F).

[h] The disutility for out-patient complications is assumed to be 1/2 the disutility for hospitalization, based on Ladabaum (2003, Ref S26) page 1024.

[i] The disutility for out-patient complications is assumed to be equal to 7 (5 to 15) days, based on Ladabaum (2003, Ref S26) Table 1.

[j] The disutility for hospitalization is assumed to be equal to the utility of active irritable bowel syndrome (0.6740 (0.6413 to 0.7049) ) minus the utility of hospitalization (0.482 (0.4 to 0.6) ), based on Ladabaum (2003, Ref S26) Table 1.

[k] =-SQRT( (((I)-(H))x(L)x(O))^2 + ((H)x((M)-(L))x(O))^2 + ((H)x(L)x((P)-(O)))^2 ), based on the assumption that the uncertainties in the terms are uncorrelated.

[l] =SQRT( (((J)-(H))x(L)x(O))^2 + ((H)x((N)-(L))x(O))^2 + ((H)x(L)x((Q)-(O)))^2 ), based on the assumption that the uncertainties in the terms are uncorrelated.

[m] The effective utility loss duration for hospitalization without surgery is assumed be 8.5 (5.5 to 14.5) days. This comprises 5 (3 to 7) days of hospitalization followed by 7 (5 to 15) days of recovery after hospitalization at 1/2 the disutility, based on Ladabaum (2003, Ref S26) page 1024.

[n] The effective utility loss duration for hospitalization with surgery is assumed be 23.5 (17 to 44) days. This is based 13 (10 to 30) days of hospitalization plus 21 (14 to 28) days of recovery after hospitalization at 1/2 the disutility, based on Ladabaum (2003, Ref S26) page 1024.

[o] Assumed equal to the utility of active irritable bowel syndrome (0.6740 (0.6413 to 0.7049) ), Ladabaum (2003, Ref S26) Table 1.

[p] The loss duration for SAE resulting in death is assumed to be the (undiscounted) life expectancy at the time of death. This value is assumed to be the weighted average life expectancy of 18 through 109 year old US females in 1999-2001 from Table 3 of Arias et al. (2008, Ref S3). This assumes that the risk of the SAE is independent of age.

[q] Assumed equal to the point estimate.

[r] Column total.

[s] =-SQRT(SUM((S)^2)), based on the assumption that the uncertainties in the estimated risks for each adverse event are uncorrelated.

[t] =SQRT(SUM((U)^2)), based on the assumption that the uncertainties in the estimated risks for each adverse event are uncorrelated.

Table S12. Estimated Risk of Lotronex (alosetron) corresponding to the FDA decision to approve NDA 21-107/S005 on 2002-06-07 (Based on Serious Adverse Events observed in Clinical Trials and Postmarketing Data).

| | (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) | (I) | (J) | (K) | (L) | (M) | (N) | (O) | (P) | (Q) | (R) | (S) | (T) | (U) | (V) | (W) | (X) | (Y) | (Z) | (AA) | (AB) | (AC) | (AD) | (AE) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Serious Adverse Event (SAE) | Estimated Number of Patients | Reported Number of SAE | Estimated Adverse Event Reporting Rate | | | Estimated Absolute Risk | | | Estimated Risk Relative to Background | | | Estimated Percentage of SAE Attributable to Background | | | Estimated Net Risk | | | | | Assumed QALY Disutility | | | Assumed Loss Duration (Years) | | | Estimated Risk (QALY Lost per Alosetron Patient) | | | | |
| | | PE | | PE | LB | UB | PE =(C)/((B)x(D)) | LB | UB | PE | LB | UB | PE = 1-((J)-1)/(J) | LB | UB | PE =(G)x(1-(M)) | LB-PE | LB =(P)+(Q) | UB-PE | UB =(P)+(S) | PE | LB | UB | PE | LB | UB | PE =(P)x(U)x(X) | LB-PE | LB =(AA)+(AB) | UB-PE | UB =(AA)+(AD) |
| (1) | Constipation with impaction, partial obstruction (requiring hospitalization but not surgery) | 11,874 [a] | 9 [a,b] | 100.00% [e] | 100.00% [e] | 100.00% [e] | 0.000758 | 0.000347 [g] | 0.001438 [h] | 5.9 [j] | 0.3 [j] | 114 [j] | 16.9% [k] | 0.9% [m] | 100.0% [n] | 0.000629 | -0.000362 [o] | 0.000267 | 0.000846 [p] | 0.001475 | 0.1920 [q] | 0.0413 [q] | 0.3049 [q] | 0.023 [r] | 0.015 [r] | 0.040 [r] | 0.0000028 | -0.0000029 [s] | -0.0000001 | 0.0000046 [t] | 0.0000074 |
| (2) | Ischemic colitis, mild, non-transmural in RCT, not serious (not requiring hospitalization or surgery) | 11,874 [a] | 4 [a,c] | 100.00% [e] | 100.00% [e] | 100.00% [e] | 0.000337 | 0.000092 [g] | 0.000862 [h] | 5.9 [i] | 0.3 [i] | 114 [i] | 16.9% [k,l] | 0.9% [m] | 100.0% [n] | 0.000280 | -0.000210 [o] | 0.000069 | 0.000518 [p] | 0.000798 | 0.0960 [u] | 0.0207 [u] | 0.1525 [u] | 0.019 [v] | 0.014 [v] | 0.041 [v] | 0.0000005 | -0.0000006 [s] | -0.0000001 | 0.0000012 [t] | 0.0000017 |
| (3) | Ischemic colitis, mild, non-transmural in RCT, serious, but not requiring surgery | 11,874 [a] | 12 [a,c] | 100.00% [e] | 100.00% [e] | 100.00% [e] | 0.001011 | 0.000522 [g] | 0.001765 [h] | 5.9 [i] | 0.3 [i] | 114 [i] | 16.9% [k,l] | 0.9% [m] | 100.0% [n] | 0.000839 | -0.000437 [o] | 0.000402 | 0.001047 [p] | 0.001887 | 0.1920 [q] | 0.0413 [q] | 0.3049 [q] | 0.023 [r] | 0.015 [r] | 0.040 [r] | 0.0000038 | -0.0000038 [s] | 0.0000000 | 0.0000058 [t] | 0.0000096 |
| (4) | Serious/severe AE requiring surgery, colon repair or removal | 11,874 [a] | 2 [a,d] | 100.00% [e] | 100.00% [e] | 100.00% [e] | 0.000168 | 0.000020 [g] | 0.000608 [h] | 5.9 [i] | 0.3 [i] | 114 [i] | 16.9% [k,l] | 0.9% [m] | 100.0% [n] | 0.000140 | -0.000126 [o] | 0.000014 | 0.000391 [p] | 0.000531 | 0.1920 [q] | 0.0413 [q] | 0.3049 [q] | 0.064 [w] | 0.047 [w] | 0.120 [w] | 0.0000017 | -0.0000021 [s] | -0.0000004 | 0.0000052 [t] | 0.0000069 |
| (5) | Possible deaths (post-marketing) | 275,000 [a] | 5 [a] | 10.00% [f] | 1.00% [f] | 100.00% [f] | 0.000182 | 0.000006 [g] | 0.004243 [h] | 5.9 [i] | 0.3 [i] | 114 [i] | 16.9% [k,l] | 0.9% [m] | 100.0% [n] | 0.000151 | -0.000149 [o] | 0.000002 | 0.003376 [p] | 0.003527 | 0.6740 [x] | 0.6413 [x] | 0.7049 [x] | 32.850 [y] | 32.850 [z] | 32.850 [z] | 0.0033433 | -0.0033010 [s] | 0.0000422 | 0.0747520 [t] | 0.0780953 |
| (6) | Cumulative incidence of ischemic colitis in women receiving LOTRONEX through 3 months in IBS clinical trials. | | | | | | | | | | | | | | | 0.002000 [A] | | 0.001000 [A] | | 0.003000 [A] | | | | | | | | | | | |
| (7) | Cumulative incidence of ischemic colitis in women receiving LOTRONEX through 6 months in IBS clinical trials. | | | | | | | | | | | | | | | 0.003000 [A] | | 0.001000 [A] | | 0.004000 [A] | | | | | | | | | | | |
| (8) | **Total** | | | | | | | | | | | | | | | | | | | | | | | | | | **0.0033521** [B] | -0.0033010 [C] | **0.0000510** | 0.0747520 [D] | **0.0781041** |
| (9) | - Non-fatal | | | | | | | | | | | | | | | | | | | | | | | | | | 0.0000088 | -0.0000052 | 0.0000036 | 0.0000091 | 0.0000179 |
| (10) | - Fatal | | | | | | | | | | | | | | | | | | | | | | | | | | 0.0033433 | -0.0033010 | 0.0000422 | 0.0747520 | 0.0780953 |

Sources and notes:

AERS FDA Adverse Event Reporting System
IC Ischemic colitis
LB Lower bounds of the estimate
PE Point estimate
QALY Quality-adjusted life-years
SAE Serious adverse event
SCSC Serious complication of severe constipation
UB Upper bounds of the estimate

[a] NDA 21-107/S005 (Ref S25), PDF page 59, Table 4.
[b] There were 10 female patients treated with Alosetron that experienced SCSC and the event was 'reported as being serious' listed in Table 7 on PDF page 203 of NDA 21-107/S005 (Ref S25). The case summaries on PDF pages 2226-228 indicate that all of these SCSC were hospitialized. Of these 10 SCSC cases, patient 67694 required surgury (ibid., PDF pages 188, 226, and 310) and is counted in row (4) of this table instead of this row (1). Row (1) also includes one patient listed in Table 7 (2230) that had surgury for ileal stenosis. There is also one patient listed in Table 7 (174139) that that experienced SCSC but was not reported as serious, and this case is not counted in this table.
[c] There were 17 female patients treated with Alosetron that experienced IC listed in Table 3 on PDF page 197 of NDA 21-107/S005 (Ref S25). Of these 17 IC cases, patient #65443 required surgery (ibid., PDF pages 224, 311, and 330) and is counted in row (4) instead of rows (2) and (3). Row (3) counts 13 female patients that where classified as serious in ibid. Table 3 (11 of these patients were admitted to the hospital and the other 2 were considered to be disabling/incapacitating events), but did not require surgury. Row (2) counts the remaining 4 cases were not classified as serious in ibid. Table 3. There was also 1 male patient treated with Alosetron listed in ibid. Table 3 that is not counted in this table.
[d] There were 2 cases involving surgury, both in study 3SB30020 (NDA 21-107/S005, Ref S25, PDF page 199). Patient 65443 had an ischemic colitis SAE (ibid., PDF pages 223, 311, and 330). Patient 67694 had a SCSC SAE (ibid., PDF pages 188, 226, and 310).
[e] It is assumed that the adverse events are not underreported in the clinical trials. Therefore the reporting rate is 100%.
[f] It is assumed that the adverse events in the FDA Adverse Event Reporting System (AERS) are underreported. It is assumed that the AERS reporting rate is 10% (1% to 100%) based on a memo from Mackey to Raczkowski dated 2002-03-26 (Ref S25, PDF page 464). The reporting rate assumed by Mackey is based on Rogers et al. (1988, Ref S5) and Scott et al. (1987, Ref S4).
[g] Calculated assuming that the probabity of a reported SAE per patient has a Binomial distribution using the MATLAB binofit((D),(B)) function (Ref S1). The lower bounds was calculated by dividing the lower bounds for the binofit((D),(B)) probability estimate by (G).
[h] Calculated assuming that the probabity of a reported SAE per patient has a Binomial distribution using the MATLAB binofit((D),(B)) function (Ref S1). The upper bounds was calculated by dividing the upper bounds for the binofit((D),(B)) probability estimate by (F).
[i] The 'best estimate' was assumed to be 5.9 with a 0.3 to 114 confidence interval based on the results in the A2001, A2001, and A3002 studies (NDA 21-107/S005, Ref S25, PDF page 75).
[j] Assumed to be the same as the relative risk of ischemic colitis.
[k] Percent SAE Attributable to Background PE (M) = 1 - (Risk Relative to Background PE (J)-1)/(Risk Relative to Background PE (J)).
[l] NDA 21-107/S005 (Ref S25), PDF page 75.
[m] Percent SAE Attributable to Background LB (N) = 1 - max(Risk Relative to Background UB (L)-1,0)/(Risk Relative to Background UB (L)).
[n] Percent SAE Attributable to Background UB (O) = 1 - min(Risk Relative to Background LB (K)-1,1)/(Risk Relative to Background LB (K)).
[o] =-SQRT(( ((H)-(G))x(1-(M)))^2 + ((G)x((M)-(N)))^2 ), based on the assumption that the uncertainties in the terms are uncorrelated.
[p] =SQRT(( ((I)-(G))x(1-(M)))^2 + ((G)x((M)-(O)))^2 ), based on the assumption that the uncertainties in the terms are uncorrelated.
[q] The disutility for hospitalization is assumed to be equal to the utility of active irritable bowel syndrome (0.6740 (0.6413 to 0.7049) ) minus the utility of hospitalization (0.482 (0.4 to 0.6) ), based on Ladabaum (2003, Ref S26) Table 1.
[r] The effective utility loss duration for hospitalization without surgery is assumed be 8.5 (5.5 to 14.5) days. This comprises 5 (3 to 7) days of hospitalization followed by 7 (5 to 15) days of recovery after hospitalization at 1/2 the disutility, based on Ladabaum (2003, Ref S26) page 1024.
[s] =-SQRT( ((Q)x(U)x(X))^2 + ((P)x((V)-(U))x(X))^2 + ((P)x(U)x((Y)-(X)))^2 ), based on the assumption that the uncertainties in the terms are uncorrelated.
[t] =SQRT( ((S)x(U)x(X))^2 + ((P)x((W)-(U))x(X))^2 + ((P)x(U)x((Z)-(X)))^2 ), based on the assumption that the uncertainties in the terms are uncorrelated.
[u] The disutility for out-patient complications is assumed to be 1/2 the disutility for hospitalization, based on Ladabaum (2003, Ref S26) assumed on page 1024.
[v] The disutility for out-patient complications is assumed to be equal to 7 (5 to 15) days, based on Ladabaum (2003, Ref S26) Table 1.
[w] The effective utility loss duration for hospitalization with surgery is assumed be 23.5 (17 to 44) days. This is based on 13 (10 to 30) days of hospitalization plus 21 (14 to 28) days of recovery after hospitalization at 1/2 the disutility, based on Ladabaum (2003, Ref S26) page 1024.
[x] Assumed equal to the utility of active irritable bowel syndrome (0.6740 (0.6413 to 0.7049) ), Ladabaum (2003, Ref S26) Table 1.
[y] The loss duration for SAE resulting in death is assumed to be the (undiscounted) life expectancy at the time of death. This value is assumed to be the weighted average life expectancy of 18 through 109 year old US females in 1999-2001 from Table 3 of Arias et al. (2008, Ref S3). This assumes that the risk of the SAE is independent of age.
[z] Assumed equal to the point estimate.
[A] NDA 21-107/S005 (Ref S25), Labeling, PDF page 15. (for reference purposes, not used.)
[B] Column total.
[C] =-SQRT(SUM((AB)^2)), based on the assumption that the uncertainties in the estimated risks for each adverse event are uncorrelated.
[D] =SQRT(SUM((AD)^2)), based on the assumption that the uncertainties in the estimated risks for each adverse event are uncorrelated.

Table S13. Estimated Benefit of Lotronex (alosetron) corresponding to the FDA decision to approve NDA 21-107/S005 on 2002-06-07 (based on the results of 3 Clinical Trials).

| (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) | (I) | (J) | (K) | (L) | (M) | (N) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study | N | Quality of Life Metric | With Alosetron | With Placebo | P-Value | Reference Value | Units | Relative Change (%) =((E)-(D))/(E) | Relative Benefit (Utility) =((E)-(D))/(G) | Benefit Duration (years) | Estimated Benefit (QALY Gained per 12 Week Treatment) PE =(J)x(K) | LB | UB |
| S3BA3001 and S3BA3002 trials with diarrhea-predominant IBS | n/a | Social scale: Uncomfort | n/a | n/a | n/a | n/a | n/a | n/a | 0.19000 [a] | 0.25 [d] | 0.04750 | n/a | n/a |
| | | Social scale: Avoid | n/a | n/a | n/a | n/a | n/a | n/a | 0.15000 [a,b] | 0.25 [d] | 0.03750 | n/a | n/a |
| | | Social scale: Embarrass | n/a | n/a | n/a | n/a | n/a | n/a | 0.18000 [a] | 0.25 [d] | 0.04500 | n/a | n/a |
| | | Social scale: In Way | n/a | n/a | n/a | n/a | n/a | n/a | 0.11000 [a] | 0.25 [d] | 0.02750 | n/a | n/a |
| | | Work scale: Affected Success | n/a | n/a | n/a | n/a | n/a | n/a | 0.04000 [c] | 0.25 [d] | 0.01000 | n/a | n/a |
| | | Work scale: Less work Done | n/a | n/a | n/a | n/a | n/a | n/a | 0.05000 [c] | 0.25 [d] | 0.01250 | n/a | n/a |
| | | Work scale: Avoided Work | n/a | n/a | n/a | n/a | n/a | n/a | 0.06000 [c] | 0.25 [d] | 0.01500 | n/a | n/a |
| | | Work scale: Not Done Well | n/a | n/a | n/a | n/a | n/a | n/a | 0.06000 [c] | 0.25 [d] | 0.01500 | n/a | n/a |
| Urgency Study S3B40031 (Primary efficacy population) | 436 [e] | Median Lost Workplace Productivity | 12.75 [e,f] | 16.60 [e,f] | 0.076 [e] | 420 [g] | hours | 23.2% [f] | 0.00917 | 0.25 [e] | 0.00229 | n/a | n/a |
| | | Median Lost Workplace Productivity | 4.92 [e] | 6.84 [e] | 0.130 [e] | 100 [h] | % | 28.1% | 0.01920 | 0.25 [e] | 0.00480 | n/a | n/a |
| | | Median Lost Activity Time | 81.80 [e,f] | 78.70 [e,f] | 0.306 [e] | 840 [j] | hours | -3.9% [f] | -0.00369 | 0.25 [e] | -0.00092 | n/a | n/a |
| | | Total Median Lost Productivity | 89.80 [e,f] | 103.53 [e,f] | 0.144 [e] | 1260 [i] | hours | 13.3% [f] | 0.01090 | 0.25 [e] | 0.00272 | n/a | n/a |
| Urgency Study S3B40031 (Intent-to-treat population) | 492 [k] | Median Lost Workplace Productivity | 20.34 [f,n] | 34.08 [f,n] | <=0.05 [m] | 420 [g] | hours | 40.3% [f,n] | 0.03271 | 0.25 [k] | 0.00818 | n/a | n/a |
| | | Median Lost Activity Time | 100.64 [f,l] | 114.87 [f,l] | 0.173 [l] | 840 [j] | hours | 12.4% [f,l] | 0.01694 | 0.25 [k] | 0.00424 | n/a | n/a |
| | | Total Median Lost Productivity | 119.00 [f,m] | 155.22 [f,m] | <=0.05 [m] | 1260 [i] | hours | 23.3% [f,m] | 0.02875 | 0.25 [k] | 0.00719 | n/a | n/a |
| Minimum | | | | | | | | | | | -0.00092 | n/a | n/a |
| Average Benefit | | | | | | | | | | | **0.01590 [o]** | **0.00710 [p]** | **0.02469 [p]** |
| Maximum | | | | | | | | | | | 0.04750 | n/a | n/a |

Sources and Notes

LB Lower bounds of the estimate

PE Point estimate

QALY Quality-adjusted life-years

UB Upper bounds of the estimate

n/a Indicates the value is not available and therefore unknown.

[a] 100% minus the digitized 'Joint' value from NDA 21-107/S005 (Ref S25), PDF page 462, Figure 7. This digitized value indicates the 'anticipated benefit to be weighted against a risk of severe injury' according to the description on PDF page 459 of ibid.

[b] 100% minus the numeric value for Figure 7 reported on PDF page 459 of NDA 21-107/S005 (Ref S25).

[c] 100% minus the digitized 'Joint' value from NDA 21-107/S005 (Ref S25), PDF page 462, Figure 8. This digitized value indicates the 'anticipated benefit to be weighted against a risk of severe injury' according to the description on PDF page 459 of ibid.

[d] NDA 21-107/S005 (Ref S25), PDF page 459.

[e] NDA 21-107/S005 (Ref S25), PDF page 173, Table 10 (It is assumed that the table on PDF page 173 is a continution of the table on PDF page 172 for the Urgency Study S3B40031, and that the study indicated in the table caption on PDF page 173 is incorrect.)

[f] NDA 21-107/S005 (Ref S25), PDF page 171.

[g] Assumed to be equal to the average number of hours worked per week (35 hours/week, Ref S29) x the duration of the study (12 weeks).

[h] Assumed value.

[i] Assumed to be equal to the number of hours in a week (24 hours/day x 7 days/week) minus the average number of hours of sleep per week (63 hours/week, Ref S28), times the duration of the study (12 weeks).

[j] Assumed equal to the total number of hours awake (1260) minus the total number of hours working (420).

[k] NDA 21-107/S005 (Ref S25), PDF page 108.

[l] NDA 21-107/S005 (Ref S25), PDF page 160.

[m] NDA 21-107/S005 (Ref S25), PDF page 161.

[n] NDA 21-107/S005 (Ref S25), PDF page 162, Table 6.

[o] Column average.

[p] =95% confidence interval for the column (L) average assuming that the values are normally distributed.

Table S14. Estimated Risk of Lotronex (alosetron) by Ladabaum (2003) based on information available for NDA 21-107/S005 (2002-06-07).

| (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) | (I) | (J) | (K) | (L) | (M) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Serious Adverse Event | Overall Alosetron Complication Rate per 6 Month Treatment | Average Alosetron Treatment Duration (If There are No Complications) (Months) | Complication Type Fraction | Complication Severity Rate | SAE Complication Rate | Assumed QALY Disutility | Assumed QALY Loss Duration | | | Estimated Risk (QALY Lost per Patient that Begins Alosetron Treatment) | | |
| | | | | | | | Days at full disutility | Days at 1/2 disutility | Total Years | | | |
| | PE | PE | PE | PE | PE =(B)x(C)x(D) x(E)/6 mo | PE | PE | PE | PE =((H)+(I)/2) / 365.25 | PE =(F)x(G)x(J) | LB | UB |
| Ischaemic colitis episodes managed as out-patient | 0.004 [=D] | 3.10 [=1+5xA] | 3/4 [=E] | 30/84 [=G] | 0.0005536 | 0.09603 [=(O-Q)/2] | 7 [=R] | | 0.019 | 0.000001 | 0.000000 [a] | 0.000003 [a] |
| Ischaemic colitis episodes resulting in hospitalization without surgery or death | 0.004 [=D] | 3.10 [=1+5xA] | 3/4 [=E] | 41/84 [=H] | 0.0007565 | 0.19206 [=O-Q] | 5 [=S] | 7 [=U] | 0.023 | 0.000003 | 0.000001 [a] | 0.000008 [a] |
| Ischaemic colitis episodes resulting in surgery | 0.004 [=D] | 3.10 [=1+5xA] | 3/4 [=E] | 11/84 [=I] | 0.0002030 | 0.19206 [=O-Q] | 13 [=T] | 21 [=V] | 0.064 | 0.000003 | 0.000001 [a] | 0.000007 [a] |
| Ischaemic colitis episodes resulting in death | 0.004 [=D] | 3.10 [=1+5xA] | 3/4 [=E] | 2/84 [=J] | 0.0000369 | 0.67406 [=O] | | | 22.800 [=W] | 0.000567 | 0.000302 [a] | 0.000872 [a] |
| Severe constipation episodes managed as out-patient | 0.004 [=D] | 3.10 [=1+5xA] | 1/4 [=F] | 30/113 [=K] | 0.0001372 | 0.09603 [=(O-Q)/2] | 7 [=R] | | 0.019 | 0.000000 | 0.000000 [a] | 0.000001 [a] |
| Severe constipation episodes resulting in hospitalization without surgery or death | 0.004 [=D] | 3.10 [=1+5xA] | 1/4 [=F] | 47/113 [=L] | 0.0002149 | 0.19206 [=O-Q] | 5 [=S] | 7 [=U] | 0.023 | 0.000001 | 0.000000 [a] | 0.000002 [a] |
| Severe constipation episodes resulting in surgery | 0.004 [=D] | 3.10 [=1+5xA] | 1/4 [=F] | 34/113 [=M] | 0.0001555 | 0.19206 [=O-Q] | 13 [=T] | 21 [=V] | 0.064 | 0.000002 | 0.000001 [a] | 0.000005 [a] |
| Severe constipation episodes resulting in death | 0.004 [=D] | 3.10 [=1+5xA] | 1/4 [=F] | 2/113 [=N] | 0.0000091 | 0.67406 [=O] | | | 22.800 [=W] | 0.000141 | 0.000075 [a] | 0.000216 [a] |
| **Total** | | | | | | | | | | **0.000718** [b] | **0.000383** [a] | **0.001107** [a] |
| - Non-fatal | | | | | | | | | | 0.000010 | 0.000004 [a] | 0.000025 [a] |
| - Fatal | | | | | | | | | | 0.000708 | 0.000377 [a] | 0.001088 [a] |

| Parameters | Parameter Values Used In this Evaluation PE | LB | UB | Parameter Values from Ladabaum (2003) Table 1 PE | LB | UB |
|---|---|---|---|---|---|---|
| [A] 'Adequate relief' rate with alosetron | 42% [c] | (s.d.=2.8) [c] | | 42% [c] | (s.d.=2.8) [c] | |
| [B] 'Adequate relief' rate with standard care | 28% [c] | (s.d.=2.5) [c] | | 28% [c] | (s.d.=2.5) [c] | |
| [C] Absolute therapeutic gain with alosetron | 14% [c] | 10% [c] | 19% [c] | 14% [c] | 10% [c] | 19% [c] |
| [D] Alosetron overall complication rate per person in 6 months | 4/1000 [c] | 2/1000 [c] | 6/1000 [c] | 4/1000 [c] | 2/1000 [c] | 6/1000 [c] |
| [E] Fraction of alosetron complications resulting from ischaemic colitis | 3/4 [c] | | | 3/4 [c] | | |
| [F] Fraction of alosetron complications resulting from severe constipation | 1/4 [c] | | | 1/4 [c] | | |
| [G] Fraction of ischaemic colitis episodes managed as out-patient | 30/84 [c] | | | 30/84 [c] | | |
| [H] Fraction of ischaemic colitis episodes resulting in hospitalization without surgery or death | 41/84 [c] | | | 41/84 [c] | | |
| [I] Fraction of ischaemic colitis episodes resulting in surgery | 11/84 [c] | | | 11/84 [c] | | |
| [J] Fraction of ischaemic colitis episodes resulting in death | 2/84 [c] | | | 2/84 [c] | | |
| [K] Fraction of severe constipation episodes managed as out-patient | 30/113 [c] | | | 30/113 [c] | | |
| [L] Fraction of severe constipation episodes resulting in hospitalization without surgery or death | 47/113 [c] | | | 47/113 [c] | | |
| [M] Fraction of severe constipation episodes resulting in surgery | 34/113 [c] | | | 34/113 [c] | | |
| [N] Fraction of severe constipation episodes resulting in death | 2/113 [c] | | | 2/113 [c] | | |
| [O] Utility of active irritable bowel syndrome | **0.67406** [e] | 0.6413 [c] | 0.7049 [c] | 0.674 [c] | 0.6413 [c] | 0.7049 [c] |
| [P] Utility gain with 'adequate relief' | **0.022** [e] | 0.02 [c] | 0.0398 [c] | 0.0242 [c] | 0.02 [c] | 0.0398 [c] |
| [Q] Utility of hospitalization | 0.482 [c] | 0.4 [c] | 0.6 [c] | 0.482 [c] | 0.4 [c] | 0.6 [c] |
| [R] Duration of out-patient complication (days) | 7 [c] | 5 [c] | 15 [c] | 7 [c] | 5 [c] | 15 [c] |
| [S] Duration of hospitalization without surgery (days) | 5 [c] | 3 [c] | 7 [c] | 5 [c] | 3 [c] | 7 [c] |
| [T] Duration of hospitalization with surgery (days) | 13 [c] | 10 [c] | 30 [c] | 13 [c] | 10 [c] | 30 [c] |
| [U] Duration of recovery from hospitalization without surgery (days) | 7 [c] | 5 [c] | 15 [c] | 7 [c] | 5 [c] | 15 [c] |
| [V] Duration of recovery from hospitalization with surgery (days) | 21 [c] | 14 [c] | 28 [c] | 21 [c] | 14 [c] | 28 [c] |
| [W] Discounted life expectancy (years) | 22.8 [d] | | | 22.8 [d] | | |

Sources and Notes

LB Lower bounds of the estimate
PE Point estimate
QALY Quality-adjusted life-years
UB Upper bounds of the estimate

[a] The 95% confidence limits are based on 5000 Monta-Carlo simulations with uniformly distributed parameter values between the lower and upper bounds, except for adaquate relief rates which were normally distributed according to Ladabaum (2003, Ref S26).
[b] Column total.
[c] Parameter from Ladabaum (2003, Ref S26), Table 1.
[d] Discounted life expectancy of a 45 year old woman, from Ladabaum (2003, Ref S26), p 1023.
[e] Adjusted to match the Alosetron and standard care average QALY results in Ladabaum (2003, Ref S26), p 1025.

Table S15. Estimated Benefit of Lotronex (alosetron) by Ladabaum (2003), based on information available for NDA 21-107/S005 (2002-06-07).

| (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) | (I) | (J) | (K) | (L) | (M) | (N) | (O) | (P) | (Q) | (R) | (S) | (T) | (U) | (V) | (X) | (Y) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment sequence (Ladabaum (2003) Figure 1) | Branch Probability | | | | | | 4-week Trial | | | | | | 5-month Treatment | | | | | | Estimated QALY per Patient that Begins Treatment | | | | |
| | 1-Month Trial Complication | Alosetron Relief | 5-Month Treatment Complication | Life or Death | Standard Care Relief | Combined Probability | Alosetron Treatment | | | Standard Care | | | Alosetron Treatment | | | Standard or Alternative Care | | | Alosetron Treatment | Std. or Alt. Care | Total QALY | | |
| | | | | | | | Utility | Duration (months) | QALY | Utility | Duration (months) | QALY | Utility | Duration (months) | QALY | Utility | Duration (months) | QALY | | | | | |
| | PE | PE | PE | PE | PE | PE =(B)x(C)x(D)x(E)x(F) | PE | PE | PE =(G)x(H)x(I)/12 | PE | PE | PE =(G)x(K)x(L)/12 | PE | PE | PE =(G)x(N)x(O)/12 | PE | PE | PE =(G)x(Q)x(R)/12 | PE =(J)+(P) | PE =(M)+(S) | PE =(T)+(U) | LB | UB |
| Alosetron - 4 week trial w no complication - adequate relief - no complication | 0.999333 =1-D/6 | 0.42 =A | 0.996667 =1-Dx5/6 | 1 | 1 | 0.418321 | 0.6961 =O+P | 1 [a] | 0.024265 | | | 0.000000 | 0.6961 =O+P | 5 [a] | 0.121324 | | | 0.000000 | 0.145588 | 0.000000 | 0.145588 | 0.130343 [c] | 0.171086 [c] |
| Alosetron - 4 week trial w no complication - adequate relief - complication - live - adequate relief | 0.999333 =1-D/6 | 0.42 =A | 0.003333 =Dx5/6 | 0.977718 =1-ExJ-FxN | 0.28 =B | 0.000383 | 0.6961 =O+P | 1 [a] | 0.000022 | | | 0.000000 | 0.6961 =O+P | 2.5 [b] | 0.000056 | 0.6961 =O+P | 2.5 [b] | 0.000056 | 0.000078 | 0.000056 | 0.000133 | 0.000068 [c] | 0.000220 [c] |
| Alosetron - 4 week trial w no complication - adequate relief - complication - live - no adequate relief | 0.999333 =1-D/6 | 0.42 =A | 0.003333 =Dx5/6 | 0.977718 =1-ExJ-FxN | 0.72 =1-B | 0.000985 | 0.6961 =O+P | 1 [a] | 0.000057 | | | 0.000000 | 0.6961 =O+P | 2.5 [b] | 0.000143 | 0.6741 =O | 2.5 [b] | 0.000138 | 0.000200 | 0.000138 | 0.000338 | 0.000179 [c] | 0.000537 [c] |
| Alosetron - 4 week trial w no complication - adequate relief - complication - die | 0.999333 =1-D/6 | 0.42 =A | 0.003333 =Dx5/6 | 0.022282 =ExJ+FxN | 1 | 0.000031 | 0.6961 =O+P | 1 [a] | 0.000002 | | | 0.000000 | 0.6961 =O+P | 2.5 [b] | 0.000005 | | | 0.000000 | 0.000006 | 0.000000 | 0.000006 | 0.000003 [c] | 0.000010 [c] |
| Alosetron - 4 week trial w no complication - no adequate relief | 0.999333 =1-D/6 | 0.58 =1-A | 1 | 1 | 1 | 0.579613 | 0.6741 =O | 1 [a] | 0.032558 | | | 0.000000 | | | | 0.6741 =O | 5 [a] | 0.162789 | 0.032558 | 0.162789 | 0.195347 | 0.179472 [c] | 0.218524 [c] |
| Alosetron - 4 week trial w complication - live - adequate relief w conventional care | 0.000667 =D/6 | 1 | 1 | 0.977718 =1-ExJ-FxN | 0.28 =B | 0.000183 | 0.6961 =O+P | 0.5 [b] | 0.000005 | 0.6961 =O+P | 0.5 [b] | 0.000005 | | | | 0.6961 =O+P | 5 [a] | 0.000053 | 0.000005 | 0.000058 | 0.000064 | 0.000033 [c] | 0.000102 [c] |
| Alosetron - 4 week trial w complication - live - no adequate relief w conventional care | 0.000667 =D/6 | 1 | 1 | 0.977718 =1-ExJ-FxN | 0.72 =1-B | 0.000469 | 0.6961 =O+P | 0.5 [b] | 0.000014 | 0.6741 =O | 0.5 [b] | 0.000013 | | | | 0.6741 =O | 5 [a] | 0.000132 | 0.000014 | 0.000145 | 0.000159 | 0.000085 [c] | 0.000242 [c] |
| Alosetron - 4 week trial w complication - die (adequate relief before death) | 0.000667 =D/6 | 1 | 1 | 0.022282 =ExJ+FxN | 0.28 =B | 0.000004 | 0.6961 =O+P | 0.5 [b] | 0.000000 | | | 0.000000 | | | | 0.6961 =O+P | 2.5 [b] | 0.000001 | 0.000000 | 0.000001 | 0.000001 | 0.000000 [c] | 0.000001 [c] |
| Alosetron - 4 week trial w complication - die (no adequate relief before death) | 0.000667 =D/6 | 1 | 1 | 0.022282 =ExJ+FxN | 0.72 =1-B | 0.000011 | 0.6741 =O | 0.5 [b] | 0.000000 | | | 0.000000 | | | | 0.6741 =O | 2.5 [b] | 0.000002 | 0.000000 | 0.000002 | 0.000002 | 0.000001 [c] | 0.000003 [c] |
| Alosetron total | | | | | | 1.000000 [b] | | | | | | | | | | | | | 0.178449 [b] | 0.163188 [b] | **0.341638** [b] | **0.341734** [c,d] | **0.358886** [c] |
| Standard care - 4 week trial - adequate relief | 1 | 1 | 1 | 1 | 0.28 =B | 0.280000 | | | 0.000000 | 0.6961 =O+P | 1 [a] | 0.016241 | | | 0.000000 | 0.6961 =O+P | 5 [a] | 0.081207 | 0.000000 | 0.097448 | 0.097448 | 0.082909 [c] | 0.117898 [c] |
| Standard care - 4 week trial - no adequate relief | 1 | 1 | 1 | 1 | 0.72 =1-B | 0.720000 | | | 0.000000 | 0.6741 =O | 1 [a] | 0.040444 | | | 0.000000 | 0.6741 =O | 5 [a] | 0.202218 | 0.000000 | 0.242662 | 0.242662 | 0.229881 [c] | 0.265740 [c] |
| Standard care total | | | | | | 1.000000 [b] | | | | | | | | | | | | | 0.000000 [b] | 0.340110 [b] | **0.340110** [b] | **0.339893** [c] | **0.356463** [c] |
| Estimated Benefit (QALY Gained per Patient that begins Alosetron Treatment) | | | | | | | | | | | | | | | | | | | | | **0.001528** | **0.000867** [c] | **0.003572** [c] |

| Parameters | Parameter Values Used In This Evaluation PE | LB | UB | Parameter Values from Ladabaum (2003, Ref S26) PE | LB | UB |
|---|---|---|---|---|---|---|
| [A] 'Adequate relief' rate with alosetron | 42% [f] | (s.d.=2.8) [f] | | 42% [f] | (s.d.=2.8) [f] | |
| [B] 'Adequate relief' rate with standard care | 28% [f] | (s.d.=2.5) [f] | | 28% [f] | (s.d.=2.5) [f] | |
| [C] Absolute therapeutic gain with alosetron | 14% [f] | 10% [f] | 19% [f] | 14% [f] | 10% [f] | 19% [f] |
| [D] Alosetron overall complication rate per person in 6 months | 4/1000 [f] | 2/1000 [f] | 6/1000 [f] | 4/1000 [f] | 2/1000 [f] | 6/1000 [f] |
| [E] Fraction of alosetron complications resulting from ischaemic colitis | 3/4 [f] | | | 3/4 [f] | | |
| [F] Fraction of alosetron complications resulting from severe constipation | 1/4 [f] | | | 1/4 [f] | | |
| [G] Fraction of ischaemic colitis episodes managed as out-patient | 30/84 [f] | | | 30/84 [f] | | |
| [H] Fraction of ischaemic colitis episodes resulting in hospitalization without surgery or death | 41/84 [f] | | | 41/84 [f] | | |
| [I] Fraction of ischaemic colitis episodes resulting in surgery | 11/84 [f] | | | 11/84 [f] | | |
| [J] Fraction of ischaemic colitis episodes resulting in death | 2/84 [f] | | | 2/84 [f] | | |
| [K] Fraction of severe constipation episodes managed as out-patient | 30/113 [f] | | | 30/113 [f] | | |
| [L] Fraction of severe constipation episodes resulting in hospitalization without surgery or death | 47/113 [f] | | | 47/113 [f] | | |
| [M] Fraction of severe constipation episodes resulting in surgery | 34/113 [f] | | | 34/113 [f] | | |
| [N] Fraction of severe constipation episodes resulting in death | 2/113 [f] | | | 2/113 [f] | | |
| [O] Utility of active irritable bowel syndrome | **0.67406** [h] | 0.6413 [f] | 0.7049 [f] | 0.674 [f] | 0.6413 [f] | 0.7049 [f] |
| [P] Utility gain with 'adequate relief' | **0.022** [h] | 0.02 [f] | 0.0398 [f] | 0.0242 [f] | 0.02 [f] | 0.0398 [f] |
| [Q] Utility of hospitalization | 0.482 [f] | 0.4 [f] | 0.6 [f] | 0.482 [f] | 0.4 [f] | 0.6 [f] |
| [R] Duration of out-patient complication (days) | 7 [f] | 5 [f] | 15 [f] | 7 [f] | 5 [f] | 15 [f] |
| [S] Duration of hospitalization without surgery (days) | 5 [f] | 3 [f] | 7 [f] | 5 [f] | 3 [f] | 7 [f] |
| [T] Duration of hospitalization with surgery (days) | 13 [f] | 10 [f] | 30 [f] | 13 [f] | 10 [f] | 30 [f] |
| [U] Duration of recovery from hospitalization without surgery (days) | 7 [f] | 5 [f] | 15 [f] | 7 [f] | 5 [f] | 15 [f] |
| [V] Duration of recovery from hospitalization with surgery (days) | 21 [f] | 14 [f] | 28 [f] | 21 [f] | 14 [f] | 28 [f] |
| [W] Discounted life expectancy (years) | 22.8 [g] | | | 22.8 [g] | | |

Check

| | (AA) | (AB) QALY | (AC) Risk | (AD) Net QALY =(AB)-(AC) | (AE) Ladabaum | (AF) Difference |
|---|---|---|---|---|---|---|
| (A1) | Alosetron | 0.341638 [i] | 0.00071775 [k] | 0.340920 | 0.34092 [l] | 0.000000 |
| (A2) | Standard care | 0.340110 [j] | | 0.340110 | 0.34011 [l] | 0.000000 |
| =(A1)-(A2) | Benefit | 0.001528 | | 0.000810 | 0.00081 [l] | 0.000000 |

Sources and Notes

LB Lower bounds of the estimate
PE Point estimate
QALY Quality-adjusted life-years
UB Upper bounds of the estimate

[a] It was assumed that the treatment or care was for the entire duration of the treatment phase.
[b] It was assumed that the probability of a complication was constant throughout the treatment phase, therefore on average the complication occurred halfway through the treatment phase.
[c] The 95% confidence limits are based on 5000 Monta-Carlo simulations with uniformly distributed parameter values between the lower and upper bounds, except for adaquate relief rates which were normally distributed according to Ladabaum (2003, Ref S26).
[d] Column subtotal.
[e] The point estimate is outside the 95% confidence interval. This is attributed to the point estimate for parameter P being near the lower range of assumed values.
[f] Parameter from Ladabaum (2003, Ref S26), Table 1.
[g] Discounted life expectancy of a 45 year old woman, from Ladabaum (2003, Ref S26), p 1023.
[h] Adjusted to match the Alosetron and standard care average QALY results in Ladabaum (2003, Ref S26), p 1025.
[i] =Estimated total combined Quality Adjusted Life-Years for Alosetron treatments from column (V) in the Benefits Estimate Table
[j] =Estimated total combined Quality Adjusted Life-Years for standard care from column (V) in the Benefits Estimate Table
[k] =Estimated Quality Adjusted Life-Years lost for Alosetron treatments from column (K) in the 'Lotronex-Risk (Ladabaum)' table.
[l] Ladabaum (2003, Ref S26), p 1025.

Table S16. Estimated Risk of Lotronex (alosetron) corresponding to the FDA decision to approve NDA 21-107/S005 on 2002-06-07 (Based on the Ladabaum (2003) probability model).

| (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) | (I) | (J) | (K) | (L) | (M) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Serious Adverse Event | Overall Alosetron Complication Rate per 6 Month Treatment | Average Alosetron Treatment Duration (If There are No Complications) (Months) | Complication Type Fraction | Complication Severity Rate | SAE Complication Rate | Assumed QALY Disutility | Assumed QALY Loss Duration | | | Estimated Risk (QALY Lost per Patient that Begins Alosetron Treatment) | | |
| | | | | | | | Days at full disutility | Days at 1/2 disutility | Total Years | | | |
| | PE | PE | PE | PE | PE =(B)x(C)x(D) x(E)/6 mo | PE | PE | PE | PE =((H)+(I)/2) / 365.25 | PE =(F)x(G)x(J) | LB | UB |
| Ischaemic colitis episodes managed as out-patient | 0.004 [=D] | 3.10 [=1+5xA] | 3/4 [=E] | 30/84 [=G] | 0.0005536 | 0.09603 [=(O-Q)/2] | 7 [=R] | | 0.019 | 0.000001 | 0.000000 [a] | 0.000003 [a] |
| Ischaemic colitis episodes resulting in hospitalization without surgery or death | 0.004 [=D] | 3.10 [=1+5xA] | 3/4 [=E] | 41/84 [=H] | 0.0007565 | 0.19206 [=O-Q] | 5 [=S] | 7 [=U] | 0.023 | 0.000003 | 0.000001 [a] | 0.000008 [a] |
| Ischaemic colitis episodes resulting in surgery | 0.004 [=D] | 3.10 [=1+5xA] | 3/4 [=E] | 11/84 [=I] | 0.0002030 | 0.19206 [=O-Q] | 13 [=T] | 21 [=V] | 0.064 | 0.000003 | 0.000001 [a] | 0.000007 [a] |
| Ischaemic colitis episodes resulting in death | 0.004 [=D] | 3.10 [=1+5xA] | 3/4 [=E] | 2/84 [=J] | 0.0000369 | 0.67406 [=O] | | | 32.850 [=W] | 0.000817 | 0.000435 [a] | 0.001252 [a] |
| Severe constipation episodes managed as out-patient | 0.004 [=D] | 3.10 [=1+5xA] | 1/4 [=F] | 30/113 [=K] | 0.0001372 | 0.09603 [=(O-Q)/2] | 7 [=R] | | 0.019 | 0.000000 | 0.000000 [a] | 0.000001 [a] |
| Severe constipation episodes resulting in hospitalization without surgery or death | 0.004 [=D] | 3.10 [=1+5xA] | 1/4 [=F] | 47/113 [=L] | 0.0002149 | 0.19206 [=O-Q] | 5 [=S] | 7 [=U] | 0.023 | 0.000001 | 0.000000 [a] | 0.000002 [a] |
| Severe constipation episodes resulting in surgery | 0.004 [=D] | 3.10 [=1+5xA] | 1/4 [=F] | 34/113 [=M] | 0.0001555 | 0.19206 [=O-Q] | 13 [=T] | 21 [=V] | 0.064 | 0.000002 | 0.000001 [a] | 0.000005 [a] |
| Severe constipation episodes resulting in death | 0.004 [=D] | 3.10 [=1+5xA] | 1/4 [=F] | 2/113 [=N] | 0.0000091 | 0.67406 [=O] | | | 32.850 [=W] | 0.000202 | 0.000108 [a] | 0.000310 [a] |
| **Total** | | | | | | | | | | **0.001030** [b] | **0.000549** [a] | **0.001579** [a] |
| - Non-fatal | | | | | | | | | | 0.000010 | 0.000004 [a] | 0.000026 [a] |
| - Fatal | | | | | | | | | | 0.001020 | 0.000543 [a] | 0.001562 [a] |

| Parameters | Parameter Values Used In this Evaluation PE | LB | UB | Parameter Values from Ladabaum (2003) Table 1 PE | LB | UB |
|---|---|---|---|---|---|---|
| [A] 'Adequate relief' rate with alosetron | 42% [c] | (s.d.=2.8) [c] | | 42% [c] | (s.d.=2.8) [c] | |
| [B] 'Adequate relief' rate with standard care | **0%** [f] | **(s.d.=0)** [f] | | 28% [c] | (s.d.=2.5) [c] | |
| [C] Absolute therapeutic gain with alosetron | **42%** [g] | | | 14% [c] | 10% [c] | 19% [c] |
| [D] Alosetron overall complication rate per person in 6 months | 4/1000 [c] | 2/1000 [c] | 6/1000 [c] | 4/1000 [c] | 2/1000 [c] | 6/1000 [c] |
| [E] Fraction of alosetron complications resulting from ischaemic colitis | 3/4 [c] | | | 3/4 [c] | | |
| [F] Fraction of alosetron complications resulting from severe constipation | 1/4 [c] | | | 1/4 [c] | | |
| [G] Fraction of ischaemic colitis episodes managed as out-patient | 30/84 [c] | | | 30/84 [c] | | |
| [H] Fraction of ischaemic colitis episodes resulting in hospitalization without surgery or death | 41/84 [c] | | | 41/84 [c] | | |
| [I] Fraction of ischaemic colitis episodes resulting in surgery | 11/84 [c] | | | 11/84 [c] | | |
| [J] Fraction of ischaemic colitis episodes resulting in death | 2/84 [c] | | | 2/84 [c] | | |
| [K] Fraction of severe constipation episodes managed as out-patient | 30/113 [c] | | | 30/113 [c] | | |
| [L] Fraction of severe constipation episodes resulting in hospitalization without surgery or death | 47/113 [c] | | | 47/113 [c] | | |
| [M] Fraction of severe constipation episodes resulting in surgery | 34/113 [c] | | | 34/113 [c] | | |
| [N] Fraction of severe constipation episodes resulting in death | 2/113 [c] | | | 2/113 [c] | | |
| [O] Utility of active irritable bowel syndrome | **0.67406** [e] | 0.6413 [c] | 0.7049 [c] | 0.674 [c] | 0.6413 [c] | 0.7049 [c] |
| [P] Utility gain with 'adequate relief' | **0.022** [e] | 0.02 [c] | 0.0398 [c] | 0.0242 [c] | 0.02 [c] | 0.0398 [c] |
| [Q] Utility of hospitalization | 0.482 [c] | 0.4 [c] | 0.6 [c] | 0.482 [c] | 0.4 [c] | 0.6 [c] |
| [R] Duration of out-patient complication (days) | 7 [c] | 5 [c] | 15 [c] | 7 [c] | 5 [c] | 15 [c] |
| [S] Duration of hospitalization without surgery (days) | 5 [c] | 3 [c] | 7 [c] | 5 [c] | 3 [c] | 7 [c] |
| [T] Duration of hospitalization with surgery (days) | 13 [c] | 10 [c] | 30 [c] | 13 [c] | 10 [c] | 30 [c] |
| [U] Duration of recovery from hospitalization without surgery (days) | 7 [c] | 5 [c] | 15 [c] | 7 [c] | 5 [c] | 15 [c] |
| [V] Duration of recovery from hospitalization with surgery (days) | 21 [c] | 14 [c] | 28 [c] | 21 [c] | 14 [c] | 28 [c] |
| [W] Discounted life expectancy (years) | **32.85** [h] | | | 22.8 [d] | | |

Sources and Notes

LB Lower bounds of the estimate
PE Point estimate
QALY Quality-adjusted life-years
UB Upper bounds of the estimate

[a] The 95% confidence limits are based on 5000 Monta-Carlo simulations with uniformly distributed parameter values between the lower and upper bounds, except for adaquate relief rates which were normally distributed according to Ladabaum (2003, Ref S26).

[b] Column total.

[c] Parameter from Ladabaum (2003, Ref S26), Table 1.

[d] Discounted life expectancy of a 45 year old woman, from Ladabaum (2003, Ref S26), p 1023.

[e] Adjusted to match the Alosetron and standard care average QALY results in Ladabaum (2003, Ref S26), p 1025.

[f] Assume no alosetron patients have adequate relief because the box warning in the label indicates: 'LOTRONEX is indicated only for women with severe diarrhea-predominant IBS who have failed to respond to conventional therapy' (NDA 21-107/S005, Ref S25, PDF page 10).

[g] ='Adequate relief' rate with alosetron-'Adequate relief' rate with standard care.

[h] The loss duration for SAE resulting in death is assumed to be the (undiscounted) life expectancy at the time of death. This value is assumed to be the weighted average life expectancy of 18 through 109 year old US females in 1999-2001 from Table 3 of Arias et al. (2008, Ref S3). This assumes that the risk of the SAE is independent of age.

Table S17. Estimated Benefit of Lotronex (alosetron) corresponding to the FDA decision to approve NDA 21-107/S005 on 2002-06-07 (Based on the Ladabaum (2003) probability model).

| (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) | (I) | (J) | (K) | (L) | (M) | (N) | (O) | (P) | (Q) | (R) | (S) | (T) | (U) | (V) | (X) | (Y) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment sequence (Ladabaum (2003) Figure 1) | Branch Probability | | | | | | 4-week Trial | | | | | | 5-month Treatment | | | | | | Estimated QALY per Patient that Begins Treatment | | | | |
| | | | | | | | Alosetron Treatment | | | Standard Care | | | Alosetron Treatment | | | Standard or Alternative Care | | | | | | | |
| | 1-Month Trial Complication | Alosetron Relief | 5-Month Treatment Complication | Life or Death | Standard Care Relief | Combined Probability | Utility | Duration (months) | QALY | Utility | Duration (months) | QALY | Utility | Duration (months) | QALY | Utility | Duration (months) | QALY | Alosetron Treatment | Std. or Alt. Care | Total QALY | | |
| | PE | PE | PE | PE | PE | PE =(B)x(C)x(D) x(E)x(F) | PE | PE | PE =(G)x(H) x(I)/12 | PE | PE | PE =(G)x(K) x(L)/12 | PE | PE | PE =(G)x(N) x(O)/12 | PE | PE | PE =(G)x(Q) x(R)/12 | PE =(J)+(P) | PE =(M)+(S) | PE =(T)+(U) | LB | UB |
| Alosetron - 4 week trial w no complication - adequate relief - no complication | 0.999333 =1-D/6 | 0.42 =A | 0.996667 =1-Dx5/6 | 1 | 1 | 0.418321 | 0.6961 =O+P | 1 [a] | 0.024265 | | | 0.000000 | 0.6961 =O+P | 5 [a] | 0.121324 | | | 0.000000 | 0.145588 | 0.000000 | 0.145588 | 0.130517 [c] | 0.170887 [c] |
| Alosetron - 4 week trial w no complication - adequate relief - complication - live - adequate relief | 0.999333 =1-D/6 | 0.42 =A | 0.003333 =Dx5/6 | 0.977718 =1-ExJ-FxN | 0.00 =B | 0.000000 | 0.6961 =O+P | 1 [a] | 0.000000 | | | 0.000000 | 0.6961 =O+P | 2.5 [b] | 0.000000 | 0.6961 =O+P | 2.5 [b] | 0.000000 | 0.000000 | 0.000000 | 0.000000 | 0.000000 [c] | 0.000000 [c] |
| Alosetron - 4 week trial w no complication - adequate relief - complication - live - no adequate relief | 0.999333 =1-D/6 | 0.42 =A | 0.003333 =Dx5/6 | 0.977718 =1-ExJ-FxN | 1.00 =1-B | 0.001368 | 0.6961 =O+P | 1 [a] | 0.000079 | | | 0.000000 | 0.6961 =O+P | 2.5 [b] | 0.000198 | 0.6741 =O | 2.5 [b] | 0.000192 | 0.000278 | 0.000192 | 0.000470 | 0.000249 [c] | 0.000737 [c] |
| Alosetron - 4 week trial w no complication - adequate relief - complication - die | 0.999333 =1-D/6 | 0.42 =A | 0.003333 =Dx5/6 | 0.022282 =ExJ+FxN | 1 | 0.000031 | 0.6961 =O+P | 1 [a] | 0.000002 | | | 0.000000 | 0.6961 =O+P | 2.5 [b] | 0.000005 | | | 0.000000 | 0.000006 | 0.000000 | 0.000006 | 0.000003 [c] | 0.000010 [c] |
| Alosetron - 4 week trial w no complication - no adequate relief | 0.999333 =1-D/6 | 0.58 =1-A | 1 | 1 | 1 | 0.579613 | 0.6741 =O | 1 [a] | 0.032558 | | | 0.000000 | | | | 0.6741 =O | 5 [a] | 0.162789 | 0.032558 | 0.162789 | 0.195347 | 0.179268 [c] | 0.218921 [c] |
| Alosetron - 4 week trial w complication - live - adequate relief w conventional care | 0.000667 =D/6 | 1 | 1 | 0.977718 =1-ExJ-FxN | 0.00 =B | 0.000000 | 0.6961 =O+P | 0.5 [b] | 0.000000 | 0.6961 =O+P | 0.5 [b] | 0.000000 | | | | 0.6961 =O+P | 5 [a] | 0.000000 | 0.000000 | 0.000000 | 0.000000 | 0.000000 [c] | 0.000000 [c] |
| Alosetron - 4 week trial w complication - live - no adequate relief w conventional care | 0.000667 =D/6 | 1 | 1 | 0.977718 =1-ExJ-FxN | 1.00 =1-B | 0.000652 | 0.6961 =O+P | 0.5 [b] | 0.000019 | 0.6741 =O | 0.5 [b] | 0.000018 | | | | 0.6741 =O | 5 [a] | 0.000183 | 0.000019 | 0.000201 | 0.000220 | 0.000118 [c] | 0.000331 [c] |
| Alosetron - 4 week trial w complication - die (adequate relief before death) | 0.000667 =D/6 | 1 | 1 | 0.022282 =ExJ+FxN | 0.00 =B | 0.000000 | 0.6961 =O+P | 0.5 [b] | 0.000000 | | | 0.000000 | | | | 0.6961 =O+P | 2.5 [b] | 0.000000 | 0.000000 | 0.000000 | 0.000000 | 0.000000 [c] | 0.000000 [c] |
| Alosetron - 4 week trial w complication - die (no adequate relief before death) | 0.000667 =D/6 | 1 | 1 | 0.022282 =ExJ+FxN | 1.00 =1-B | 0.000015 | 0.6741 =O | 0.5 [b] | 0.000000 | | | 0.000000 | | | | 0.6741 =O | 2.5 [b] | 0.000002 | 0.000000 | 0.000002 | 0.000003 | 0.000001 [c] | 0.000004 [c] |
| Alosetron total | | | | | | 1.000000 [b] | | | | | | | | | | | | | 0.178449 [b] | 0.163185 [b] | **0.341634 [b]** | **0.341681 [c,d]** | **0.359012 [c]** |
| Standard care - 4 week trial - adequate relief | 1 | 1 | 1 | 1 | 0.00 =B | 0.000000 | | | 0.000000 | 0.6961 =O+P | 1 [a] | 0.000000 | | | 0.000000 | 0.6961 =O+P | 5 [a] | 0.000000 | 0.000000 | 0.000000 | 0.000000 | 0.000000 [c] | 0.000000 [c] |
| Standard care - 4 week trial - no adequate relief | 1 | 1 | 1 | 1 | 1.00 =1-B | 1.000000 | | | 0.000000 | 0.6741 =O | 1 [a] | 0.056172 | | | 0.000000 | 0.6741 =O | 5 [a] | 0.280858 | 0.000000 | 0.337030 | 0.337030 | 0.336068 [c] | 0.352045 [c] |
| Standard care total | | | | | | 1.000000 [b] | | | | | | | | | | | | | 0.000000 [b] | 0.337030 [b] | **0.337030 [b]** | **0.336068 [c]** | **0.352045 [c]** |
| Estimated Benefit (QALY Gained per Patient that begins Alosetron Treatment) | | | | | | | | | | | | | | | | | | | | | **0.004604** | **0.004140 [c]** | **0.008560 [c]** |

| Parameters | Parameter Values Used In This Evaluation PE | LB | UB | Parameter Values from Ladabaum (2003, Ref S26) PE | LB | UB |
|---|---|---|---|---|---|---|
| [A] 'Adequate relief' rate with alosetron | 42% [f] | (s.d.=2.8) [f] | | 42% [f] | (s.d.=2.8) [f] | |
| [B] 'Adequate relief' rate with standard care | **0%** [i] | **(s.d.=0)** | | 28% [f] | (s.d.=2.5) [f] | |
| [C] Absolute therapeutic gain with alosetron | **42%** [j] | | | 14% [f] | 10% [f] | 19% [f] |
| [D] Alosetron overall complication rate per person in 6 months | 4/1000 [f] | 2/1000 [f] | 6/1000 [f] | 4/1000 [f] | 2/1000 [f] | 6/1000 [f] |
| [E] Fraction of alosetron complications resulting from ischaemic colitis | 3/4 [f] | | | 3/4 [f] | | |
| [F] Fraction of alosetron complications resulting from severe constipation | 1/4 [f] | | | 1/4 [f] | | |
| [G] Fraction of ischaemic colitis episodes managed as out-patient | 30/84 [f] | | | 30/84 [f] | | |
| [H] Fraction of ischaemic colitis episodes resulting in hospitalization without surgery or death | 41/84 [f] | | | 41/84 [f] | | |
| [I] Fraction of ischaemic colitis episodes resulting in surgery | 11/84 [f] | | | 11/84 [f] | | |
| [J] Fraction of ischaemic colitis episodes resulting in death | 2/84 [f] | | | 2/84 [f] | | |
| [K] Fraction of severe constipation episodes managed as out-patient | 30/113 [f] | | | 30/113 [f] | | |
| [L] Fraction of severe constipation episodes resulting in hospitalization without surgery or death | 47/113 [f] | | | 47/113 [f] | | |
| [M] Fraction of severe constipation episodes resulting in surgery | 34/113 [f] | | | 34/113 [f] | | |
| [N] Fraction of severe constipation episodes resulting in death | 2/113 [f] | | | 2/113 [f] | | |
| [O] Utility of active irritable bowel syndrome | **0.67406** [h] | 0.6413 [f] | 0.7049 [f] | 0.674 [f] | 0.6413 [f] | 0.7049 [f] |
| [P] Utility gain with 'adequate relief' | **0.022** [h] | 0.02 [f] | 0.0398 [f] | 0.0242 [f] | 0.02 [f] | 0.0398 [f] |
| [Q] Utility of hospitalization | 0.482 [f] | 0.4 [f] | 0.6 [f] | 0.482 [f] | 0.4 [f] | 0.6 [f] |
| [R] Duration of out-patient complication (days) | 7 [f] | 5 [f] | 15 [f] | 7 [f] | 5 [f] | 15 [f] |
| [S] Duration of hospitalization without surgery (days) | 5 [f] | 3 [f] | 7 [f] | 5 [f] | 3 [f] | 7 [f] |
| [T] Duration of hospitalization with surgery (days) | 13 [f] | 10 [f] | 30 [f] | 13 [f] | 10 [f] | 30 [f] |
| [U] Duration of recovery from hospitalization without surgery (days) | 7 [f] | 5 [f] | 15 [f] | 7 [f] | 5 [f] | 15 [f] |
| [V] Duration of recovery from hospitalization with surgery (days) | 21 [f] | 14 [f] | 28 [f] | 21 [f] | 14 [f] | 28 [f] |
| [W] Life expectancy (years) | **32.85** [k] | | | 22.8 [g] | | |

Sources and Notes

LB Lower bounds of the estimate
PE Point estimate
QALY Quality-adjusted life-years
UB Upper bounds of the estimate

[a] It was assumed that the treatment or care was for the entire duration of the treatment phase.
[b] It was assumed that the probability of a complication was constant throughout the treatment phase, therefore on average the complication occurred halfway through the treatment phase.
[c] The 95% confidence limits are based on 5000 Monta-Carlo simulations with uniformly distributed parameter values between the lower and upper bounds, except for adaquate relief rates which were normally distributed according to Ladabaum (2003, Ref S26).
[d] Column subtotal.
[e] The point estimate is outside the 95% confidence interval. This is attributed to the point estimate for parameter P being near the lower range of assumed values.
[f] Parameter from Ladabaum (2003, Ref S26), Table 1.
[g] Discounted life expectancy of a 45 year old woman, from Ladabaum (2003, Ref S26), p 1023.
[h] Adjusted to match the Alosetron and standard care average QALY results in Ladabaum (2003, Ref S26), p 1025.
[i] Assume no alosetron patients have adequate relief because the box warning in the label indicates: 'LOTRONEX is indicated only for women with severe diarrhea-predominant IBS who have failed to respond to conventional therapy' (NDA 21-107/S005, Ref S25, PDF page 10).
[j] ='Adequate relief' rate with alosetron-'Adequate relief' rate with standard care.
[k] The loss duration for SAE resulting in death is assumed to be the (undiscounted) life expectancy at the time of death. This value is assumed to be the weighted average life expectancy of 18 through 109 year old females in 1999-2001 from Table 3 of Arias et al. (2008, Ref S3). This assumes that the risk of the SAE is independent of age.

Table S18. Estimated Risk and Benefit of Lotronex (alosetron) corresponding to the FDA decision to approve NDA 21-107/S005 on 2002-06-07 (Based on the Lynd (2010) simulation model).

| (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) | (I) | (J) | (K) | (L) | (M) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Severity | Estimated Risk (-Harm) (RVALY per Patient Treated over 52 Weeks) | | | | Estimated Benefit (RVALY per Patient Treated over 52 Weeks) | | | | Estimated Net Benefit (RVALY per Patient Treated over 52 Weeks) | | | |
| | PE | SE | LB | UB | PE | SE | LB | UB | PE | SE | LB | UB |
| Mild | 0.0008 [c] | 0.000153 [f] | 0.0005 [c] | 0.0011 [c] | 0.01877 [d] | 0.009383 [i] | 0.00038 [j] | 0.03716 [k] | 0.01797 [a] | 0.009383 [h] | -0.00055 [a] | 0.03623 [a] |
| Moderate | 0.0008 [c] | 0.000153 [f] | 0.0005 [c] | 0.0011 [c] | 0.03078 [d] | 0.006714 [i] | 0.01762 [j] | 0.04394 [k] | 0.02998 [a] | 0.006714 [h] | 0.01705 [a] | 0.04337 [a] |
| **Severe** | **0.0008 [c]** | 0.000153 [f] | **0.0005 [c]** | **0.0011 [c]** | **0.03678 [d]** | 0.006449 [i] | **0.02414 [j]** | **0.04942 [k]** | **0.03598 [a]** | 0.006449 [h] | **0.02349 [a]** | **0.04877 [a]** |
| All | 0.0008 [b] | 0.000153 [f] | 0.0005 [b] | 0.0011 [b] | 0.0312 [b] | 0.007526 [g] | 0.0167 [b] | 0.0462 [b] | 0.0304 [a,e] | 0.007526 [h] | 0.0159 [a] | 0.0454 [a] |

Sources and Notes

LB Lower bounds of the estimate

PE Point estimate

RVALY Relative value-adjusted life-years.

SE Standard error of the estimate

UB Upper bounds of the estimate

[a] Lynd et al. (2010, Ref S27), pp 411.

[b] Lynd et al. (2010, Ref S27), pp 414.

[c] Assumed equal to the combined estimate because Figure 3 in Lynd et al. (2010, Ref S27) suggests that the risk are uncorrelated with the benefits.

[d] =(B)+(J).

[e] =(F)-(B).

[f] =((E)-(D))/(2x1.96)

[g] =((I)-(H))/(2x1.96)

[h] =((M)-(L))/(2x1.96)

[i] Assumed=(K) because the uncertainty in risk (C) is relatively small.

[j] =(F)+1.96x(G).

[k] =(F)-1.96x(G).

### *Meridia (sibutramine hydrochloride monohydrate)*

This section describes the estimated risks and benefits of Meridia based on information in Refs S3, S6, S15, and S30 through S40. The calculation steps and values are provided in Table S19 through Table S22 and the supporting sources and notes.

Meridia was originally approved by the FDA in November 1997 for the management of obesity in patients with an initial body mass index (BMI) of ≥30 kg/m² or ≥27 kg/m² in the presence of other risk factors (e.g., hypertension, diabetes, and hyperlipidemia) (NDA 20-632, Refs S32 and S33). Part of the approval package (NDA 20-632, Ref S33, Part 4, PDF pages 221-226, 272-305) included the results of a risk-benefit analysis by the drug sponsor in terms of the estimated deaths and lives saved per million Meridia patient-years. The sponsor estimated the cardiovascular disease (CVD)-related mortality risks of Meridia attributable to an average of 2 mm Hg increase in the systolic and diastolic blood pressure to be 32 and 42 deaths per million patient-years, respectively, assuming a BMI of 30 and 32, respectively (Part 4, PDF page 302). Because there was no estimate of the lower bounds for these estimates, it was assumed that the estimated risk of Meridia exposure was **32 (32, 42)** deaths per million Meridia patient-years (see Table S19).

The sponsor also estimated the life-saving benefits of Meridia resulting from weight reduction in the avoidance of CVD-related and non-CVD deaths to be 235 lives saved per million Meridia patient-years, based on weight loss results from Study SB 1047 (NDA 20-632, Ref S33, Part 4, PDF pages 293 and 300) (reproduced in Table S20). If the weight loss results from Study BPI 852 are used to extend this analysis, then the estimated benefits are 207 lives saved per million Meridia patient-years. Because there was no estimate of the upper bounds for this estimate, it

was assumed that the estimated benefit of Meridia at the time of approval was **235 (207, 235)** lives saved per million patient-years.

Meridia was subsequently withdrawn from the market in October 2010 based on information about the risk of non-fatal myocardial infarction (MI) and non-fatal stroke from the Sibutramine Cardiovascular Outcomes Trial (SCOUT) (Riley and Jefferson, 2010, Ref S39). The revised estimate of the risks of Meridia at the time of withdrawal were quantified in terms of QALY lost per Meridia patient because the results of SCOUT study reported in James *et al* (2010, Ref S37) indicated that main AEs of concern were non-fatal MI and non-fatal stroke, and not mortality. The SCOUT study indicated that the increased risk of cardiovascular death and death from any cause was death due to Meridia use was small and not statistically significant. Risks due to other AEs were assumed to be relatively small. The duration for the quality of life lost after the adverse events was assumed to be equal to the life expectancy at the time of the AE, in which the average age of the patient when the AE occurs is 65 (53, 77) years. This estimate was based on the age of the patients in the SCOUT study when treatment began (63.3 (51.1, 75.5)) plus ½ of the treatment duration (3.4 years), assuming that the risk of an AE was constant during over the duration of the treatment. Therefore the quality of life lost duration after the adverse event was assumed to be 17.8 (10.0, 27.3) years based on the US life expectancy in 1999-2001 (Arias et al., 2008, Ref S3, Table 1). Based on these assumptions, the resulting estimated risk of Meridia was **0.0559 (0.0080, 0.1190)** QALY lost per patient (see Table S21).

The revised estimate of the benefits of Meridia were quantified in terms of QALY gained for direct comparison with the revised risk estimates. The QALY gained was estimated based on health-related quality of life information reported by Di Francesco *et al* (2007, Ref S36). Three

different estimates were obtained based on different assumed values for the duration of the health related benefit (see Table S22).

The first two benefit estimates were based on the assumption that the duration for the quality of life gained is to be equal to the life expectancy at the time the treatment began, which was assumed to be 41.9 (20.5, 63.3) years based on Di Francesco et al (2007, Ref S36). Thus, the QALY benefit duration was assumed to be 37.1 (19.3, 56.9) years based on US life expectancy tables. The resulting estimated benefit of Meridia was **0.9923 (-0.0056, 2.0168)** QALY gained per patient. This estimate may overestimate the benefits, however, since (1) the assumed benefit duration is more than twice the assumed loss duration; and (2) patients in the study reported by Di Francesco *et al* were substantially younger on average than those in the SCOUT study.

The second benefit estimate is based on the assumption that the average age when treatment began was 63.3 years, as in the SCOUT study. The QALY benefit duration was assumed to be 19.3 (11.1, 29.0) years based on US life expectancy tables, resulting in an estimated benefit of **0.5154 (0.0108, 1.0406)** QALY gained per patient. However, this estimate may also overestimate the benefits of Meridia when compared to the estimated risks because the assumed benefit duration if the health-related benefits are only obtained during treatment (i.e., the benefits are temporary whereas the risks would continue after the treatment is stopped).

The third benefit estimate is based on the assumption that the QALY benefit duration was 3.4 years, corresponding to the average treatment in the SCOUT study. The resulting estimated benefit of Meridia of **0.0910 (0.0106, 0.1714)** QALY gained per patient. However, this may represent an underestimate of the benefits of Meridia compared to the estimated risks if the health-related benefits continue after treatment with Meridia is suspended.

The approval of Meridia was formally withdrawn in December 2010 (75 FR 80061, Ref S40).

Table S19. Estimated Risk of Meridia (Sibutramine) corresponding to the FDA decision to approve NDA 20-632 on 1997-11-22.

| (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) | (I) | (J) | (K) | (L) | (M) | (N) | (O) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Adverse Event | Increase in CVD Risk | Assumed Patient Body Mass Index | | | Relative CVD Mortality Based on Assumed BMI | | | CVD Mortality per Person-Year | | | | Estimated Risk (CVD Deaths per Sibutramine Patient-Year) | | |
| | | | | | | | | Baseline | Increase | | | | | |
| | PE | PE | LB | UB | PE | LB | UB | PE | PE =(F)x(I) | LB =(G)x(I) | UB =(H)x(I) | PE =(B)x(J) | LB =(B)x(K) | UB =(B)x(L) |
| | | | | | | | | | | | | | | |
| 2 mm Hg increase in mean population diastolic blood pressure | 5% [a] | 30 [a, b] | 30 [c] | 32 [a, d] | 2.9 [a, e] | 2.9 [c] | 3.8 [f, e] | 0.000220 [a] | 0.000638 [a] | 0.000638 | 0.000836 [a] | 0.000032 [a] | 0.000032 | 0.000042 [a] |
| Total | | | | | | | | | | | | **0.000032** [g] | **0.000032** | **0.000042** [a] |

Sources and Notes

BMI Body Mass Index

CVD Cardiovascular disease

PE Point estimate

LB Lower bounds

PE Upper bounds

[a] FDA meeting with sponsor regarding NDA 20-632 'Meridia (sibutramine hydrochloride monohydrate) Capsules' on July 25, 1996. Sponsor presentation slide. NDA 20-632 (Ref S33), Part 4 , PDF page 302.

[b] Corresponds to a 5% to <10% loss in body weight relative to a starting BMI of 32 (200 lbs and 5', 6") according to the table on PDF page 294 of op. cit., Part 4.

[c] Assumed equal to the point estimate.

[d] Corresponds to no loss in body weight relative to a starting BMI of 32 (200 lbs and 5', 6") according to the table on PDF page 294 of op. cit., Part 4.

[e] Appears to be from graph on PDF page 288 of op. cit., Part 4. The results in this figure are attributed to results for non-smokers in Figures 2 and 3 of Manson et al. (1995, Ref S30).

[f] =(L)/(I).

[g] NDA 20-632 (Ref S33), Part 4 , PDF page 304.

Table S20. Estimated Benefit of Meridia (Sibutramine) corresponding to the FDA decision to approve NDA 20-632 on 1997-11-22.

| | (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) | (I) | (J) | (K) | (L) | (M) | (N) | (O) | (P) | (Q) | (R) | (S) | (T) | (U) | (V) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Percent Loss of Body Weight | Percent of Patients Achieving this Weight Loss with 15 mg Sibutramine | | | Resultant BMI | Estimated Change Compared to a Starting BMI of 32 (200 pounds and 5' 6") [a] | | | | | | | | | | | | | | Estimated Benefit (Lives Saved per 1,000,000 Sibutramine Patient-Years) | | |
| | | | | | | All Causes of Death | | | CVD Deaths | | | | | | Non-CVD Deaths | | | | | | | |
| | | | | | | Absolute Risk of Death Relative to BMI=19 | All Cause Deaths Avoided per 1,000,000 Person-Years Achieving This Weight Loss | All Cause Deaths Avoided per 1,000,000 Sibutramine Patient Years | Absolute Risk of Death Relative to BMI=19 | CVD Deaths Avoided per 1,000,000 Person-Years Achieving This Weight Loss (No BP Adjustment) | CVD Deaths Avoided per 1,000,000 Sibutramine Patient Years (No BP Adjustment) | Lack of Blood Pressure Benefit Adjustment Factor | CVD Deaths Avoided per 1,000,000 Person-Years Achieving This Weight Loss (With BP Adjustment) | CVD Deaths Avoided per 1,000,000 Sibutramine Patient Years (With BP Adjustment) | Non-CVD Deaths Avoided per 1,000,000 Person-Years Achieving This Weight Loss (No BP Adjustment) | Non-CVD Deaths Avoided per 1,000,000 Sibutramine Patient Years (No BP Adjustment) | Lack of Blood Pressure Benefit Adjustment Factor | Non-CVD Deaths Avoided per 1,000,000 Person-Years Achieving This Weight Loss (With BP Adjustment) | Non-CVD Deaths Avoided per 1,000,000 Sibutramine Patient Years (With BP Adjustment) | | | |
| | | PE (SB 1047) | LB (BPI 852) | UB | PE | PE | PE =((F1)-(F))x1399 [g] | PE =(B)x(E) | PE | PE =((I1)-(I))x220 [i] | PE =(B)x(H) | PE | PE =(J)x(L) | PE =(K)x(L) | PE =(G)-(J) | PE =(B)x(O) | PE | PE =(O)x(Q) | PE =(P)x(Q) | PE =(N)+(S) | LB =(T)x(C)/(B) [n] | UB =(T)x(D)/(B) [n] |
| (1) | 0% to <5% | 35% [b] | 34% [b] | 35% [e] | 32.0 [a] | 2.0 [f] | 0 | 0.0 | 3.8 [f] | 0 | 0.0 | 50% [k] | 0 | 0 | 0 | 0.0 | 117/118 [l] | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| (2) | 5% to <10% [a] | 26% [c] | 29% [d] | 26% [e] | 30.0 [a] | 1.8 [f] | 279.8 [h] | 72.7 [h] | 2.9 [f,i] | 198 [j] | 51.5 [j] | 50% [k] | 99 [k] | 25.7 [k] | 81.8 | 21.3 | 117/118 [l] | 81.1 | 21.1 | 46.8 [m] | 52.2 | 46.8 |
| (3) | 10% to <15% [a] | 24% [c] | 29% [d] | 24% [e] | 28.5 [a] | 1.6 [f] | 559.6 [h] | 134.3 [h] | 1.8 [f] | 440 [j] | 105.6 [j] | 50% [k] | 220 [k] | 52.8 [k] | 119.6 | 28.7 | 117/118 [l] | 118.6 | 28.5 | 81.3 [m] | 98.2 | 81.3 |
| (4) | 15%+ [a] | 15% [c] | 8% [d] | 15% [e] | 27.0 [a] | 1.3 [f] | 979.3 [h] | 146.9 [h] | 1.4 [f] | 528 [j] | 79.2 [j] | 50% [k] | 264 [k] | 39.6 [k] | 451.3 | 67.7 | 117/118 [l] | 447.5 | 67.1 | 106.7 [m] | 56.9 | 106.7 |
| | Total Lives Saved | | | | | | | 353.9 [h,o] | | | 236.3 [j,o] | | | 118.1 [k,o] | | 117.7 [o,p] | | | 116.7 [o,q] | **234.8** [m,o] | **207.3** [o] | **234.8** [o] |

Sources and Notes

CVD Cardiovascular Disease. See NDA 20-632 (Ref S33), Part 4, PDF page 276.

PE Point estimate

LB Lower bounds

UB Upper bounds

[a] FDA meeting with sponsor regarding NDA 20-632 'Meridia (sibutramine hydrochloride monohydrate) Capsules' on 1996-07-25. Sponsor presentation slide. NDA 20-632 (Ref S33), Part 4, PDF page 294. 15 mg Sibutramine.

[b] =100%-column sum for rows (2), (3), and (4).

[c] op. cit., Part 4, PDF page 293. Study SB 1047, 15 mg Sibutramine.

[d] op. cit., Part 4, PDF page 293. Study BPI 852, 15 mg Sibutramine.

[e] Assumed equal to the point estimate because the uncertainty in the estimate is unknown.

[f] op. cit, Part 4, PDF page 288 (digitized value from the graph).

[g] =( (F1) - (F) ) x B, where B is the all cause mortality for BMI=19. B was assumed to be 1399 deaths per million per year (i.e., 1399 deaths per million person-years) in order to fit the results in op. cit, Part 4, PDF page 296. The source for this value is unknown.

[h] op. cit, Part 4, PDF page 296.

[i] =( (I1) - (I) ) x 220. The CVD mortality for BMI=19 was assumed to be 220 deaths per million per year (op. cit, Part 4, PDF page 302).

[j] op. cit, Part 4, PDF page 297.

[k] op. cit, Part 4, PDF page 298.

[l] =117 'Non-CVD deaths avoided adjusted for BP'/118 'Non-CVD deaths avoided with no BP adjustment' (op. cit, Part 4, PDF page 301). It is unknown why the two values are different and the ratio is not equal to 1.

[m] op. cit, Part 4, PDF page 300.

[n] The estimated benefit for a given loss of body weight is proportional to the percent of patients achieving the body weight loss.

[o] Column total.

[p] 118 'Non-CVD deaths avoided with no BP adjustment' (op. cit, Part 4, PDF page 301).

[q] 117 'Non-CVD deaths avoided adjusted for BP' (op. cit, Part 4, PDF page 301).

Table S21. Estimated Risk of Meridia (Sibutramine) corresponding to the FDA request on 2010-10-08 that it be withdrawn from the US market, after reviewing the results of the SCOUT study.

| (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) | (I) | (J) | (K) | (L) | (M) | (N) | (O) | (P) | (Q) | (R) | (S) | (T) | (U) | (W) | (X) | (Y) | (Z) | (AA) | (AB) | (AC) | (AD) | (AE) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Adverse Event | Sibutramine | | | Placebo | | | Estimated Net Increase in Risk per Patient due to Meridia (Sibutramine) | | | | Assumed Age to begin Treatment (years) | | | | Ass. Trmt. (years) | Assumed Age for the Adverse Event (years) | | | Assumed QALY Disuse Factor | | | Assumed Loss Duration (years) | | | Estimated Risk (QALY Lost per Sibutramine Patient) | | | | |
| | Number of | | Risk | Number of | | Risk | | | | | | | | | | | | | | | | | | | | | | | |
| | Patients | Events | PE =(B)/(C) | Patients | Events | PE =(E)/(F) | PE =(D)-(G) | SE of PE | LB | UB | PE | SD | LB | UB | PE | PE | LB | UB | PE | LB | UB | PE | LB | UB | PE =(H)x(T)x(X) | LB-PE | LB =(AA)+(AB) | UB-PE | UB =(AA)+(AD) |
| Non-fatal myocardial infarction | 4906 [a, b] | 200 [a] | 4.08% | 4898 [a, b] | 159 [a] | 3.25% | 0.83% | 0.38% [c] | 0.09% [d] | 1.57% [d] | 63.3 [e] | 6.2 [e] | 51.15 [f] | 75.45 [f] | 3.4 [e] | 65.0 [h] | 52.8 [h] | 77.2 [h] | 0.16 [i] | 0.085 [i] | 0.330 [i] | 17.77 [k] | 9.98 [k] | 27.31 [k] | 0.0236 | -0.0260 [l] | -0.0024 | 0.0352 [m] | 0.0588 |
| Non-fatal stroke | 4906 [a, b] | 127 [a] | 2.59% | 4898 [a, b] | 95 [a] | 1.94% | 0.65% | 0.30% [c] | 0.06% [d] | 1.24% [d] | 63.3 [e] | 6.2 [e] | 51.15 [f] | 75.45 [f] | 3.4 [e] | 65.0 [h] | 52.8 [h] | 77.2 [h] | 0.28 [j] | 0.075 [j] | 0.625 [j] | 17.77 [k] | 9.98 [k] | 27.31 [k] | 0.0323 | -0.0402 [l] | -0.0079 | 0.0524 [m] | 0.0847 |
| Total | | | | | | | | | | | | | | | | | | | | | | | | | **0.0559** [n] | -0.0479 [o] | **0.0080** | 0.0631 [p] | **0.1190** |

Sources and Notes

QALY Quality-adjusted life-years
PE Point estimate
SD Standard deviation (of the sample)
SE Standard error (of the point estimate)
LB Lower bounds
PE Upper bounds

[a] James et al. (2010, Ref S37), Figure 3.
[b] Patient inclusion criteria included overweight or obese, 55 years of age or older, with preexisting cardiovascular disease, type 2 diabetes mellitus, or both.
[c] =SQRT( (D)x(1-(D))/(B) + (G)x(1-(G))/(E) ) according to Eqn (2.13) in Fleiss (1981, Ref S2).
[d] =(H)±1.96x(I). See Eqn (7.6) in Fleiss (1981, Ref S2).
[e] Assumed equal to the age range of the SCOUT study subjects at screening (James et al., 2010, Ref S37, Table 1). The minimum age for the SCOUT study was 55 years. The range of ages were 51 to 88 years.
[f] =(L)±1.96x(M).
[g] Assumed equal to the mean treatment duration in the SCOUT study described in James et al. (2010, Ref S37).
[h] Assumed equal to (P)/2 years after treatment began.
[i] Assumed to be equal to 1-average of the QALY utility values following a myocardial infarction reported in Tsevat et al. (1993, Ref S6) (0.88 (0.84,0.93)), and Erickson et al. (2013, Ref S15) Table 1 (0.80 (0.50,0.90)).
[j] Assumed to be equal to 1-average of the QALY utility values following a stroke reported in Mathias et al. (1997, Ref S31) (0.64 (0.35,0.93)), and Erickson et al. (2013, Ref S15) Table 1 (0.80 (0.40,0.92)).
[k] Assumed equal to the life expectancy at the time of the adverse event ((Q),(R),(S)). Values estimated from Arias et al. (2008, Ref S3) Table 1 after rounding the age to the nearest year.
[l] =-SQRT( (((J)-(H))x(T)x(X))^2 + ((H)x((U)-(T))x(X))^2 + ((H)x(T)*((Y)-(X)))^2 ), based on the assumption that the uncertainties in the terms are uncorrelated.
[m] =-SQRT( (((K)-(H))x(T)x(X))^2 + ((H)x((W)-(T))x(X))^2 + ((H)x(T)*((Z)-(X)))^2 ), based on the assumption that the uncertainties in the terms are uncorrelated.
[n] =column total.
[o] =-SQRT(SUM((AB)^2)), based on the assumption that the uncertainties in the estimated risks for each adverse event are uncorrelated.
[p] =SQRT(SUM((AD)^2)), based on the assumption that the uncertainties in the estimated risks for each adverse event are uncorrelated.

Table S22. Estimated Benefit of Meridia (Sibutramine) corresponding to the FDA request on 2010-10-08 that it be withdrawn from the US market, after reviewing the results of the SCOUT study.

| (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) | (I) | (J) | (K) | (L) | (M) | (N) | (O) | (P) | (Q) | (R) | (S) | (T) | (U) | (V) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment | Number of Patients | IWQOL-Lite Total Score | | | | Quality of Life Utility Factor (SF-6D) | | | | Assumed Age when Health Related Benefits Begin (years) | | | | Assumed Duration of the Health Related Benefit (years) | | | Estimated Benefit (QALY Gained per Sibutramine Patient) | | | | |
| | | Baseline | | Change after 6 Mos. of Treatment | | Baseline | | Change after 6 Mos. of Treatment | | | | | | | | | | | | | |
| | PE | PE | SD [a] | PE | SD [a] | PE | SD [a] | PE | SD [a] | PE | SD [a] | LB | UB | PE | LB | UB | PE =(I)*(O) | LB-PE | LB =(R)+(S) | UB-PE | UB =(R)+(U) |
| Placebo | 155 [b, c, d] | 129.0 [b] | 19.6 [b] | -4.5 [e] | 2.0 [e] | 0.543 [f] | 0.066 [g] | 0.015 [g] | 0.007 [g] | 42.3 [h] | 11.0 [h] | 20.7 [i] | 63.9 [i] | | | | | | | | |
| Sibutramine | 154 [b, c, d] | 131.3 [b] | 18.7 [b] | -12.5 [e] | 3.0 [e] | 0.535 [f] | 0.063 [g] | 0.042 [g] | 0.010 [g] | 41.5 [h] | 10.8 [h] | 20.3 [i] | 62.7 [i] | | | | | | | | |
| Net effect (lifetime benefit, DiFrance | | 2.3 [j] | 27.1 [k] | -8.0 [j] | 3.6 [k] | -0.008 [j] | 0.091 [k] | 0.027 [j] | 0.012 [k] | 41.9 [l] | | 20.5 [l] | 63.3 [l] | 37.06 [m] | 19.25 [m] | 56.87 [m] | **0.9923** [n] | -0.9978 [o] | **-0.0056** [n] | 1.0245 [p] | **2.0168** [n] |
| Net effect (lifetime benefit, SCOUT) | | 2.3 [j] | 27.1 [k] | -8.0 [j] | 3.6 [k] | -0.008 [j] | 0.091 [k] | 0.027 [j] | 0.012 [k] | 63.3 [q] | 6.2 [q] | 51.1 [i] | 75.5 [i] | 19.25 [m] | 11.12 [m] | 29.03 [m] | **0.5154** [n] | -0.5046 [o] | **0.0108** [n] | 0.5252 [p] | **1.0406** [n] |
| Net effect (temporary benefit, SCOUT | | 2.3 [j] | 27.1 [k] | -8.0 [j] | 3.6 [k] | -0.008 [j] | 0.091 [k] | 0.027 [j] | 0.012 [k] | | | | | 3.4 [r] | 3.4 [r] | 3.4 [r] | **0.0910** [n] | -0.0804 [o] | **0.0106** [n] | 0.0804 [p] | **0.1714** [n] |

Sources and Notes

IWQOL Impact of Weight on Quality of Life-Light. A health related quality of life scale described in Kolotkin (2001, Ref S34). Possible values range from 31 (best) to 155 (poorest).

QALY Quality-adjusted life-years

PE Point estimate

SD Standard deviation (of the sample)

LB Lower bounds

UB Upper bounds

[a] It is assumed that the ± values in Di Francesco et al. (2007, Ref S36) are standard deviations of the sample.

[b] Di Francesco et al. (2007, Ref S36), Table 1.

[c] Sponsor presentation to the FDA (Ref S38), p C-34.

[d] Patient inclusion criteria included body mass index (BMI) of >=30 and <=40 kg/m 2, and age 18-65 years. Exclusion criteria included obesity of endocrine etiology, type-1 diabetes, uncontrolled type-2 diabetes, a heart rate of >100 beats/min, or uncontrolled hypertension (diastolic pressure >95 mm Hg and systolic > 160 mm Hg).

[e] Di Francesco et al. (2007, Ref S36), p 78.

[f] =0.456+0.00415*(IWQOL-Lite Score)/1.24 according to Brazier et al. (2004, Ref S35) Model 1.

[g] =0.00415*(change in IWQOL-Lite Score)/1.24 according to Brazier et al. (2004, Ref S35) Model 1.

[h] Assumed equal to the age of the patients in the Di Francesco et al. (2007, Ref S36) study population reported in Table 1. Note this age range is younger than the age range used to estimate the risks.

[i] =(K)±1.96x(L).

[j] =(PE_Sibutramine-PE_Placebo).

[k] =SQRT(SD_Sibutramine^2+SD_Pacebo^2).

[l] =(PE_Sibutramine+PE_Placebo)/2.

[m] Assumed equal to the life expectancy at the time of the treatment ((K),(M),(N)). Values estimated from Arias et al. (2008, Ref S3) Table 1 after rounding the age to the nearest year.

[n] Change in Quality of Life Utility Factor after 6 months of treatment x Duration of Health Related Benefit.

[o] =-SQRT( (-1.96*(J)x(O))^2 + ((I)x((P)-(O)))^2), based on the assumption that the uncertainty in the terms are uncorrelated.

[p] =-SQRT( (-1.96*(J)x(O))^2 + ((I)x((Q)-(O)))^2), based on the assumption that the uncertainty in the terms are uncorrelated.

[q] Assumed equal to the age range of the SCOUT study subjects at screening (James et al., 2010, Ref S37, Table 1). The minimum age for the SCOUT study was 55 years. The range of ages were 51 to 88 years.

[r] Assumed equal to the mean treatment duration in the SCOUT study described in James et al. (2010, Ref S37).

### *Redux (dexfenfluramine)*

This section describes the estimated risks and benefits of Redux based on information in Refs S3, S6, S15, S30 and S41 through S56. The calculation steps and values are provided in Table S23 through Table S28 and the supporting sources and notes.

Redux (dexfenfluramine) was originally approved in April 1996 (CDER, 1996, Ref S43) "for the "management of obesity". At the time of approval, the risks and benefits of Redux were estimated by the sponsor to be **9.6** excess deaths due to primary pulmonary hypertension (PPH) compared to **280** lives saved by weight reduction, per million person-years of Redux treatment (Ref S41, page 114; Ref S42, page 174). The risks were estimated based on preliminary results of the International Primary Pulmonary Hypertension Study (IPPHS) (Ref S41, p 104), and did not include possible neurological and psychological risks that were observed in animal toxicology studies (see Table S23 and Table S24). There was only a limited amount of information in these sources to estimate the uncertainty in the estimated risk, and no information to estimate the uncertainty in the estimated benefits.

The FDA requested the manufacturers voluntarily withdraw Redux from the US market in September 1997 (Bachorik, 1997, Ref S47) based on post-marketing safety information related to risk of valvular heart disease (VHD) associated with Redux. The risks and benefits of Redux corresponding to this decision were then estimated in terms of quality-adjusted life-years (QALYs) lost and gained, which include non-fatal risks and benefits in addition to deaths and lives saved.

The estimated risk of Redux corresponding to the US market withdrawal was quantified based on the final results of the IPPHS reported by Abenhaim et al (1996, Ref S45) and Mason and Faich (1996, Ref S46), and the risk of VHD from available information reported in the medical literature (Refs S47, S48, S50, S51, and S53). The risks of PPH were updated and expanded to include non-fatal PPH, which were estimated to be 38 cases per million person-years (Refs S45 and S46), 50% of which were assumed to be fatal. The QALY lost due to PPH fatality was estimated as the reduction in life expectancy (Arias et al. 2008, Ref S3, Table 1) assuming that the patients begin treatment at age 45 (21, 69) years and would continue treatment for the rest of their life, resulting in 0.0119 (0.0003, 0.1114) QALY lost per patient. The QALY lost due to non-fatal PPH was estimated based on an assumed PPH disutility factor times the assumed loss duration. The PPH disutility factor was assumed to be 0.51 (0.44, 0.69) based on quality of life information reported by McKenna *et al* (2008). The assumed lost duration was assumed to be 17.2 (7.5, 28.4) years, which is one-half of the assumed remaining life expectancy. This loss duration was based on the assumption that the probability of PPH occurring is constant during the treatment, and therefore is on average equal to one-half the treatment duration. The resulting estimated QALY lost per patient due to non-fatal PPH was 0.0056 (-0.0011, 0.0525) (see Table S25).

The risks of VHD requiring surgery or resulting in death were also estimated in terms of QALY lost. It was assumed that the VHD event occurred at 44 (22, 68) years based on provider-initiated (i.e., spontaneous) reports reported by Bowen *et al* (1997, Ref S50). The VHD disutility factor for non-fatal VHD requiring surgery was assumed to be 0.251 (0.093, 0.417), based on analysis of quality of life reported by Reynolds *et al* (2012, Ref S56) (see Table S26). The resulting

combined estimate of Redux risk due to fatal and non-fatal PPH and VHD is **0.8794 (0.2599, 1.8231)** (see Table S27).

The estimated benefit of Redux corresponding to the US market withdrawal was quantified based on information reported by Manson and Faich (1996, Ref S46), who reported that 280 deaths and 400 non-fatal MIs and cerebrovascular events would be prevented per million Redux patient-years due to weight loss. The estimated 280 lives saved per million patient-years is the same estimate derived prior to initial approval (Refs S41 and S42), while the benefit in QALY gained due to non-fatal MI and cerebrovascular events prevented was estimated using the same methods and benefit durations as used to estimate the risks. The QALY disutility factor was assumed to be 0.16 (0.085, 0.33) based on information in Tsevat *et al* (1993, Ref S6) and Erickson *et al* (2013, Ref S15), which yielded an estimated benefit of **0.2138 (0.0642, 0.5143)** QALY gained per Redux patient (see Table S28).

The approval of Redux was formally withdrawn in January 2007 (72 FR 4270, Ref S54).

Table S23. Estimated Risk of Redux (dexfenfluramine) corresponding to the FDA decision to approve NDA 20-344 on 1996-04-29.

| | (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) | (I) | (J) | (K) | (L) | (M) | (N) | (O) | (P) | (Q) | (R) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Adverse Event | PPH Patients | | | Control Patients | | | Relative Risk (Odds Ratio) | | | Background PPH Risk per Person-Year | | | Estimated Net Increase in Risk per Person-Year due to Redux | | | | |
| | | Number of | | Rate | Number of | | Rate | | | | | | | | | | | |
| | | Patients | AS Use > 3 months | PE =(B)/(C) | Patients | AS Use > 3 months | PE =(E)/(F) | PE | LB | UB | PE =(N)/(H) | LB | UB | PE | LB - PE | LB =(N)+(O) | UB - PE | UB =(N)+(Q) |
| (1) | Primary pulmonary hypertension | 95 [b] | n/a | n/a | 355 [b] | n/a | n/a | 10.6 [c] | 9.0 [d] | 10.6 [e] | 0.0000020 [f] | 0.0000010 [f] | 0.0000020 [f] | 0.0000192 [g] | -0.0000101 [h] | 0.0000091 | 0.000000 [i] | 0.0000192 |
| (2) | - Non-fatal | - | - | - | - | - | - | - | - | - | - | - | - | 0.0000096 [k] | -0.0000051 [k] | 0.0000045 | 0.000000 [k] | 0.0000096 |
| (3) | - Fatal | - | - | - | - | - | - | - | - | - | - | - | - | **0.0000096** [k,l] | -0.0000051 [k] | **0.0000045** | 0.000000 [k] | **0.0000096** |

Sources and Notes

AE Adverse Event
AS Appetite Suppressant (includes Redux (dexfenluramine), fenfluramine, diethylpropion, clobenzorex, fenproporex, phenmetrazine, and compounds)
LB Lower bounds of the estimate
PE Point estimate
PPH Primary pulmonary hypertension
PY Person-Year
SD Standard deviation (of the data sample)
UB Upper bounds of the estimate
- Not applicable
n/a Not available

[a] The basic approach begins with Manson and Faich (1996, Ref S46). The following are the main exceptions:
- The estimated risks were recomputed using information presented to the FDA in September and November 1995 (Refs S41 and S42). Confidence intervals are are also computed.
- The results have been extended to include the effects of both fatal and non-fatal PPH on quality adjusted life-years lost.
- The estimate does not include possible neurological and psychological risks that were observed in animal studies (e.g., Ref S42, pp 9-10).

[b] Faish presentation (on behalf of the sponsor) to the FDA on 1995-09-28 (Ref S41, p 104). Also Faish presentation to the FDA on 1995-11-16 (Ref S42, p 169).
[c] Faish presentation (on behalf of the sponsor) to the FDA on 1995-09-28 (Ref S41, p 104). Also Faish presentation to the FDA on 1995-11-16 (Ref S42, p 170). Includes other appetite suppressants.
[d] A preliminary evaluation of the IPPH data before the approval of Redux (Cruzan, S., 1996, Ref S44).
[e] Assumed equal to the point estimate because the uncertainty is unknown.
[f] Faish presentation (on behalf of the sponsor) to the FDA on 1995-09-28 (Ref S41, p 110).
[g] Faish presentation (on behalf of the sponsor) to the FDA on 1995-09-28 (Ref S41, p 110) and equal to ((H)-1) x (K). Also Faish presentation to the FDA on 1995-11-16 (Ref S42, p 170), rounded to '1.9 excess cases per 100,000 exposures.'
[h] =-SQRT( (((I)-(H))x(K))^2 + (((H)-1)x((L)-(K)))^2 ), based on the assumption that the uncertainties in the terms are uncorrelated.
[i] =SQRT( (((J)-(H))x(K))^2 + (((H)-1)x((M)-(K)))^2 ), based on the assumption that the uncertainties in the terms are uncorrelated.
[j] Abenhaim et al. (1996, Ref S45), Table 1.
[k] =Row (1) x 50% based on an assumption in the Faish presentation (on behalf of the sponsor) to the FDA on 1995-09-28 that the fatality rate for patients with PPH is 50% (Ref S41, p 110).
[l] Faish presentation (on behalf of the sponsor) to the FDA on 1995-09-28 (Ref S41, pp 110, 114).

Table S24. Estimated Benefit of Redux (dexfenfluramine) corresponding to the FDA decision to approve NDA 20-344 on 1996-04-29.

| | (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) |
|---|---|---|---|---|---|---|---|---|
| | Percent Loss of Body Weight | Estimated Percent of Patients Achieving this Weight Loss with Dexfenfluramine | Resultant BMI | Risk of Death Relative to BMI=19 | Estimated Change Compared to a Starting BMI of 32 (191 pounds and 5' 5") [a] | | | Estimated Benefit (Lives Saved per 1,000,000 Dexfenfluramine Patient-Years) |
| | | | | | Percent Change | Deaths Avoided per 1,000,000 Person-Years Achieving This Weight Loss | | |
| | | PE | PE =32x(1-(A)) | PE | PE =((D1)-(D)) | PE =((E))x1075 [f] | PE =ROUND((F),10) | PE =(B)x(G) |
| (1) | 0% | 40% [b] | 32.0 | 2.0 [d] | 0 | 0.0 | | 0.0 |
| (2) | 5% [c] | 20% [c] | 30.4 | 1.9 [d] | 10.0% | 107.5 | 110 [e] | 22.0 [g] |
| (3) | 10% [c] | 20% [c] | 28.8 | 1.6 [d] | 40.0% | 430.0 [e] | 430 [e] | 86.0 [g] |
| (4) | 15% [c] | 20% [c] | 27.2 | 1.2 [d] | 80.0% [e] | 860.0 [e] | 860 [e] | 172.0 [g] |
| | Total Lives Saved | | | | | | | **280.0** [g,i] |

Sources and Notes

LB Lower bounds of the estimate

PE Point estimate

UB Upper bounds of the estimate

[a] Faish presentation (on behalf of the sponsor) to the FDA on 1995-09-28 (Ref S41, p 112).

[b] =100%-column sum for rows (2), (3), and (4).

[c] Faish presentation (on behalf of the sponsor) to the FDA on 1995-09-28 (Ref S41, p 113). Also Faish presentation to the FDA on 1995-11-16 (Ref S42, p 174).

[d] Values reproduce the results in (E). The results were attributed to Manson et al. (1995, Ref S30). The values appear to be the 'multivariate relative risk' estimates for women who never smoked in the lower left graph in Figure 2 of ibid.

[e] Faish presentation (on behalf of the sponsor) to the FDA on 1995-09-28 (Ref S41, p 112).

[f] The baseline value of 1075 fatalities per million person years=860 excess lives lost per year/80%.

[g] Faish presentation (on behalf of the sponsor) to the FDA on 1995-09-28 (Ref S41, pp 113-114). Also Faish presentation to the FDA on 1995-11-16 (Ref S42, p 174). Some of the results in the 1995-11-16 presentation are rounded to the nearest integer per 100,000 patient-years.

[h] The estimated benefit for a given loss of body weight is proportional to the percent of patients achieving the body weight loss.

[i] Column total.

Table S25. Estimated Risk of Redux (dexfenfluramine) shortly after the FDA decision to approve NDA 20-344 on 1996-04-29 (Manson and Faich method with Abenhaim baseline risk, plus non-fatal PPH).

| | (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) | (I) | (J) | (K) | (L) | (M) | (N) | (O) | (P) | (Q) | (R) | (S) | (T) | (U) | (W) | (X) | (Y) | (Z) | (AA) | (AB) | (AC) | (AD) | (AE) | (AF) | (AG) | (AH) | (AI) | (AJ) | (AK) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Adverse Event | PPH Patients | | | Control Patients | | | Relative Risk | | | Background PPH Risk | | | Estimated Net Increase in Risk | | | | | Assumed Patient Age to Begin Treatment | | | | Assumed Treatment Duration | | | Assumed QALY | | | Assumed Loss Duration | | | Estimated Risk | | | | |
| | | Number of | | Rate | Number of | | Rate | (Adjusted Odds Ratio) | | | per Person-Year | | | per Person-Year due to Redux | | | | | (years) | | | | (years) | | | Disuse Factor | | | (years) | | | (QALY Lost per Patient) | | | | |
| | | Patients | AS Use > 3 months | PE =(B)/(C) | Patients | AS Use > 3 months | PE =(E)/(F) | PE | LB | UB | PE | LB | UB | PE | LB - PE | LB =(N)+(O) | UB - PE | UB =(N)+(Q) | PE | Sample SD | LB =(S)-1.96x(T) | UB =(S)+1.96x(T) | PE | LB | UB | PE | LB | UB | PE =(X)/2 [l] | LB =(Y)/2 [l] | UB =(Z)/2 [l] | PE | LB-PE | LB | UB-PE | UB |
| (1) | Primary pulmonary hypertension | 95 [b] | 18 [b] | 18.9% [b] | 355 [b] | 5 [b] | 1.4% [b] | 23.1 [b,c] | 6.9 [b] | 77.7 [b] | 0.0000017 [d] | 0.0000010 [d] | 0.0000024 [d] | 0.000038 [e] | -0.000032 [f] | 0.000006 | 0.000094 [g] | 0.000132 | 44.7 [h] | 12.3 [h] | 20.6 | 68.8 | - | - | - | - | - | - | - | - | - | - | | - | | - |
| (2) | - Non-fatal | - | - | - | - | - | - | - | - | - | - | - | - | 0.000019 [i] | -0.000016 [i] | 0.000003 | 0.000047 [i] | 0.000066 | 44.7 [h] | 12.3 [h] | 20.6 | 68.8 | 34.34 [j] | 14.95 [j] | 56.87 [j] | 0.51 [k] | 0.44 [k] | 0.69 [k] | 17.17 [l] | 7.48 [l] | 28.44 [l] | 0.0056 [m] | -0.0066 [n] | -0.0011 [o] | 0.0101 [p] | 0.0525 [q] |
| (3) | - Fatal | - | - | - | - | - | - | - | - | - | - | - | - | 0.000019 [i] | -0.000016 [i] | 0.000003 | 0.000047 [i] | 0.000066 | 44.7 [h] | 12.3 [h] | 20.6 | 68.8 | - | - | - | - | - | - | - | - | - | 0.0119 [r] | -0.0115 [s] | 0.0003 [r] | 0.0996 [t] | 0.1114 [r] |
| | **Total** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | **0.0175** [u] | -0.0133 [v] | **-0.0007** [o] | 0.1001 [w] | **0.1639** [q] |

Sources and Notes

AE Adverse Event
AS Appetite Suppressant (includes Redux (dexfenluramine), fenfluramine, diethylpropion, clobenzorex, fenproporex, phenmetrazine, and compounds)
LB Lower bounds of the estimate
PE Point estimate
PPH Primary pulmonary hypertension
PY Person-Year
SD Standard deviation of the data sample
UB Upper bounds of the estimate
- Not applicable

[a] The basic approach begins with Manson and Faich (1996, Ref S46). The following are the main exceptions:
- The estimated risks were recomputed using the original data from Abenhaim et al. (1996, Ref S45). This also includes the Abenhaim estimate for baseline risk per person-year, which is better supported and different than the estimate used by Manson and Faich (see note d). Confidence intervals are are also computed.
- The estimated net increase in risk per person-year excludes the baseline risk. Manson et al. reported the 'absolute risk'.
- The results have been extended to include the effects of both fatal and non-fatal PPH on quality adjusted life-years lost.

[b] Abenhaim et al. (1996, Ref S45), Table 3 (duration of use > 3 months). Includes other appetite suppressants.
[c] Cruzan, S., (1996, Ref S44).
[d] Abenhaim et al. (1996, Ref S45), p 613. Manson and Faich (1996, Ref S46) assumed the background PPH risk was 'about 1.2 per million person-years' but did not provide a source or confidence intervals.
[e] =((H)-1)x(K).
[f] =-SQRT( (((I)-(H))x(K))^2 + (((H)-1)x((L)-(K)))^2 ), based on the assumption that the uncertainties in the terms are uncorrelated.
[g] =SQRT( (((J)-(H))x(K))^2 + (((H)-1)x((M)-(K)))^2 ), based on the assumption that the uncertainties in the terms are uncorrelated.
[h] Abenhaim et al. (1996, Ref S45) Table 1.
[i] Manson and Faich (1996, Ref S46) assumed a 50 percent mortality rate for patients with PPH.
[j] The treatment duration is assumed to be equal to the life expectancy of the patient at the time the patient begins treatment, which depends on the age of the patient. The values were estimated from Arias et al. (2008, Ref S3) Table 1 after rounding the age the patient begins treatment (i.e., (S) ((U),(W)) ) to the nearest integer value.
[k] Assumed equal to 1-the utility values for 'Quite severe', 'Very severe', and 'Moderate' pulmonary hypertension in McKenna et al. (2008, Ref S55).
[l] The loss duration is assumed to be equal to 1/2 the life expectancy of the patient at the time the patient begins treatment, which depends on the age of the patient. The values were estimated from Arias et al. (2008, Ref S3) Table 1 after rounding the age the patient begins treatment (i.e., (S) ((U),(W)) ) to the nearest integer value.
[m] =(N)x(X)x(AA)x(AD).
[n] =-SQRT( ((O)x(X)x(AA)x(AD))^2 + ((N)x((Y)x(AE)-(X)x(AD))x(AA))^2 + ((N)x(X)x((AB)-(AA))x(AD))^2 ), based on the assumption that the uncertainties in the terms are uncorrelated.
[o] =(AG)+(AH).
[p] =SQRT( ((P)x(X)x(AA)x(AD))^2 + ((N)x((Z)x(AF)-(X)x(AD))x(AA))^2 + ((N)x(X)x((AC)-(AA))x(AD))^2 ), based on the assumption that the uncertainties in the terms are uncorrelated.
[q] =(AG)+(AJ).
[r] Assumed equal to the reduction in the Life expectancy in years relative to the baseline life expectancy in Arias et al. (2008, Ref S3) Table 1 if the annual probabiity of death due to PPH between the age the treatment began (i.e., (S) ((U),(W)) ) and 109 years old is ((N) ((O),(Q)) ).
[s] =(AI)+(AG).
[t] =(AK)+(AG).
[u] =column total.
[v] =-SQRT(SUM((AH)^2)), based on the assumption that the uncertainties in the estimated risks for the adverse events are uncorrelated.
[w] =SQRT(SUM((AJ)^2)), based on the assumption that the uncertainties in the estimated risks for the adverse events are uncorrelated.

Table S26. Supporting information for the Redux-Risks-Revised analysis - Estimate of Quality of Life Utility after Aortic Valve Replacement.

| (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) | (I) | (J) | (K) | (L) | (M) | (N) | (O) | (P) | (Q) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Cohort | Baseline | | | | | | After 1 Year | | | | | | | | | |
| | Number of Patients | EQ-5D Utility | | | | | Number of Patients | Δ EQ-5D Utility | | | | | EQ-5D Utility | | | |
| | | PE | Sample SD | SE of PE =(D)/SQRT((B)) | LB =(C)-1.96x(E) | UB =(C)+1.96x(E) | | PE | Sample SD | SE of PE =(J)/SQRT((H)) | LB | UB | PE | SE of PE | LB =(N)-1.96x(O) | UB =(N)+1.96x(O) |
| PARTNER Cohort TF | 216 [a] | 0.660 [a] | 0.210 [b] | 0.014 | 0.632 | 0.688 | 129 [c] | 0.08 [c] | 0.232 [e] | 0.020 [f] | 0.040 [c] | 0.120 [c] | 0.740 [g] | 0.025 [h] | 0.554 | 0.923 |
| PARTNER Cohort TA | 84 [a] | 0.720 [a] | 0.170 [b] | 0.019 | 0.684 | 0.756 | 54 [d] | 0.05 [d] | 0.262 [e] | 0.036 [f] | -0.020 [d] | 0.120 [d] | 0.770 [g] | 0.040 [h] | 0.723 | 0.992 |
| Combined Estimate | 300 [i] | 0.677 [j] | 0.200 [j] | 0.012 | 0.654 | 0.699 | 183 [i] | 0.07 [j] | 0.241 [j] | 0.018 [k] | 0.036 [l] | 0.106 [l] | 0.749 [j] | 0.021 [h] | 0.583 | 0.907 |

Sources and Notes

LB Lower bounds of the estimate

PE Point estimate (i.e., the mean value)

SD Standard deviation of the data sample

SE Standard error of the point estimate

UB Upper bounds of the estimate

[a] Reynolds et al. (2012, Ref S56) Table 1.

[b] It is assumed that the SD values reported in Reynolds et al. (2012, Ref S56) Table 1 are the standard deviations of the data, not the standard deviations of the mean value (i.e., PE). Otherwise the SD values of the data would be greater than 1, which is not possible for a scale between 0 and 1.

[c] Reynolds et al. (2012, Ref S56) Table 2.

[d] Reynolds et al. (2012, Ref S56) Table 3.

[e] =SQRT((H))x(K).

[f] =((M)-(L))/(2x1.96).

[g] =(C)+(I).

[h] =SQRT((D)^2+(K)^2), assuming that the variation in the change in EQ-5D is independent of variation in the baseline EQ-5D.

[i] =Column total.

[j] =pooled estimate assuming the data have equal means and variances.

[k] =(J)/SQRT((H)).

[l] =(I)±1.96x(K).

Table S27. Estimated Risk of Redux (dexfenfluramine) corresponding to the FDA decision to request the manufacturers to withdraw Dexfenfluramine from the US Market on 1997-09-15.

| (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) | (I) | (J) | (K) | (L) | (M) | (N) | (O) | (P) | (Q) | (R) | (S) | (T) | (U) | (W) | (X) | (Y) | (Z) | (AA) | (AB) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Adverse Event | Redux (dexfenfluramine) | | | | | Baseline | | | Estimated Net Increase in Risk per Patient due to Redux (dexfenfluramine) | | | | Assumed Age for Adverse Event (years) | | | Assumed QALY Disuse Factor | | | Assumed Loss Duration (years) | | | Estimated Risk (QALY Lost per Patient) | | | | |
| | Number of | | Risk | | | Number of | | Risk | | | | | | | | | | | | | | | | | | |
| | Patients | Events | PE =(B)/(C) | LB | UB | Subjects | Events | PE =(G)/(H) | PE =(D)-(I) | SE of PE | LB | UB | PE | LB | UB | PE | LB | UB | PE | LB | UB | PE =(J)x(Q)x(T) | LB-PE | LB =(X)+(Y) | UB-PE | UB =(X)+(AA) |
| Primary pulmonary hypertension | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | | - | | - |
| - Non-fatal | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 0.0056 [a] | -0.0066 [a] | -0.0011 [a] | 0.0101 [a] | 0.0525 [a] |
| - Fatal | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 0.0119 [a] | -0.0115 [a] | 0.0003 [a] | 0.0996 [a] | 0.1114 [a] |
| Valvular heart disease | 291 [b,c] | 92 [c,d] | 31.6% [e] | 26.3% [f] | 37.3% [f] | 4000 [h] | | 1.0% [h] | 30.6% | 2.73% [i] | 25.26% [j] | 35.97% [j] | | | | | | | | | | - | | - | | - |
| - Aortic regurgitation | 291 [b,c] | 74 [g] | 25.4% | 20.5% [f] | 30.8% [f] | | | | 25.4% | | | | - | - | - | - | - | - | - | - | - | - | | - | | - |
| - Mitral regurgitation | 291 [c] | 21 [g] | 7.2% | 4.5% [f] | 10.8% [f] | | | | 7.2% | | | | - | - | - | - | - | - | - | - | - | - | | - | | - |
| - Requires surgery (non-fatal) | 113 [d,k] | 24 [d,k] | 21.2% | 14.1% [f] | 29.9% [f] | | | | 6.5% [l] | | 3.6% [l] | 10.8% [l] | 44 [k] | 22 [k] | 68 [k] | 0.251 [m] | 0.093 [m] | 0.417 [m] | 35.24 [o] | 15.64 [o] | 55.92 [o] | 0.5755 [p] | -0.5495 [q] | 0.0260 | 0.6328 [r] | 1.2083 |
| - Fatal | 113 [d,k] | 3 [d,k] | 2.7% | 0.6% [f] | 7.6% [f] | | | | 0.8% [l] | | 0.1% [l] | 2.7% [l] | 44 [k] | 22 [k] | 68 [k] | 1 [n] | 1 [n] | 1 [n] | 35.24 [o] | 15.64 [o] | 55.92 [o] | 0.2864 | -0.2859 [q] | 0.0005 | 0.6928 [r] | 0.9793 |
| Total | | | | | | | | | | | | | | | | | | | | | | **0.8794** | -0.6196 [s] | **0.2599** | 0.9436 [t] | **1.8231** |

Sources and Notes

AR Aortic regurgitation
LB Lower bounds of the estimate
MR Mitral regurgitation
PE Point estimate
PPH Primary pulmonary hypertension
SE Standard error of the point estimate
UB Upper bounds of the estimate
- Not applicable

[a] Values from Table S25.
[b] Ref S48 indicates the FDA received 'reports from five physicians who had performed heart studies (echocardiograms) on [291] patients who had received fen-phen or dexfen-phen and did not have symptoms of heart disease'. Kolata (1997, Ref S49) indicates the average age of the patients was 45 years old.
[c] Pi-Sunyer (1999, Ref S51).
[d] According to Bowen et al. (1997, Ref S50), a qualifiying 'case of fenfluramine- or dexfenfluramine-associated cardiac valvulopathy was defined as documented AR of mild or greater severity and/or MR of moderate or greater severity after exposure to these drugs '.
[e] Refs S47 and S48 (rounded to 30%), and Pi-Sunyer (1999, Ref S51) (rounded to 32%).
[f] Calculated using the Matlab Statistics Toolbox Binofit function (Ref S1).
[g] Pi-Sunyer (1999, Ref S51), percentage of patients with abnormal echocariograms having aortic or mitral regurgitation x 92 patients found with abnormal echocariograms, rounded to the nearest integer value.
[h] Results of the CARDIA study for healty adult subjects summarized in Kolata (1997, Ref S49) and Weissman (2001, Ref S53). Kolata indicates the subjects ranged from 23 to 45 years old. Weissman indicates the subjects ranged from 23 to 35 years old.
[i] =SQRT( (D)x(1-(D))/(B) + (I)x(1-(I))/(G) ) according to Eqn (2.13) in Fleiss (1981, Ref S1).
[j] =(J)±1.96x(K). See Eqn (7.6) in Fleiss (1981, Ref S1).
[k] 'Provider initiated (i.e., 'spontaneous') reports' described in Bowen et al. (1997, Ref S50).
[l] =Net increase in the risk of Valvular heart disease meeting the severity criteria ((J)=30.6%) x the relative risk of surgury or death in column (D).
[m] Assumed equal to 1-the average EQ-5D Utility Factor 1 year after surgical aortic valve replacement reported in Reynolds et al. (2012, Ref S56). See Table S26.
[n] The disuse factor for death is 1 by definition.
[o] Assumed equal to the life expectancy at the time of the adverse event ((N),(O),(P)). Values estimated from Arias et al. (2008, Ref S3) Table 1.
[p] Does not include the cost for surgury. Elixhauser (1999, Ref S52.) Table 2 indicates the mean charge for heart valve procedures in 1996 was $65,730.
[q] =-SQRT( (((L)-(J))x(Q)x(T))^2 + ((J)x((R)-(Q))x(T))^2 + ((J)x(Q)x((U)-(T)))^2 ), based on the assumption that the uncertainties in the terms are uncorrelated.
[r] =SQRT( (((M)-(J))x(Q)x(T))^2 + ((J)x((S)-(Q))x(T))^2 + ((J)x(Q)x((W)-(T)))^2 ), based on the assumption that the uncertainties in the terms are uncorrelated.
[s] =-SQRT(SUM((Y)^2)), based on the assumption that the uncertainties in the estimated risks for the adverse event are uncorrelated.
[t] =SQRT(SUM((AA)^2)), based on the assumption that the uncertainties in the estimated risks for the adverse event are uncorrelated.

Table S28. Estimated Risk of Redux (dexfenfluramine) corresponding to the FDA decision to request the manufacturers to withdraw Dexfenfluramine from the US Market on 1997-09-15.

| (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) | (I) | (J) | (K) | (L) | (M) | (N) | (O) | (P) | (Q) | (R) | (S) | (T) | (U) | (V) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Adverse Event Prevented | Estimated Net Benefit per Person-Year due to Redux | | | Assumed Patient Age to Begin Treatment (years) | | | | Assumed Treatment Duration (years) | | | Assumed QALY Disuse Factor | | | Assumed Benefit Duration (years) | | | Estimated Benefit (QALY Gained per Patient) | | | | |
| | PE | LB | UB | PE | Sample SD | LB =(E)-1.96x(F) | UB =(E)+1.96x(F) | PE | LB | UB | PE | LB | UB | PE =(I)/2 [f] | LB =(J)/2 [f] | UB =(K)/2 [f] | PE | LB-PE | LB | UB-PE | UB |
| Non-fatal myocardial infarctions and cerebrovasular events | 0.000400 [a] | 0.000400 [b] | 0.000400 [b] | 44.7 [c] | 12.3 [c] | 20.6 | 68.8 | 34.34 [d] | 14.95 [d] | 56.87 [d] | 0.16 [e] | 0.085 [e] | 0.33 [e] | 17.17 [f] | 7.48 [f] | 28.44 [f] | 0.0377 [g] | -0.0349 [h] | 0.0028 [i] | 0.0532 [j] | 0.0910 [k] |
| Deaths | 0.000280 [l,a] | 0.000280 [b] | 0.000280 [b] | 44.7 [c] | 12.3 [c] | 20.6 | 68.8 | - | - | - | - | - | - | - | - | - | 0.1760 [m] | -0.1454 [n] | 0.0306 [m] | 0.2958 [o] | 0.4718 [m] |
| **Total** | | | | | | | | | | | | | | | | | **0.2138** [p] | -0.1495 [q] | **0.0642** [i] | 0.3006 [r] | **0.5143** [k] |

Sources and Notes

AE Adverse Event
LB Lower bounds of the estimate
PE Point estimate
PY Person-Year
SD Standard deviation of the data sample
UB Upper bounds of the estimate
- Not applicable

[a] Manson and Faich (1996, Ref S46).
[b] Assumed equal to the point estimate because the uncertainty in the estimate is unknown.
[c] Assumed to be the same as in study reported in Abenhaim et al. (1996, Ref S45), Table 1.
[d] The treatment duration is assumed to be equal to the life expectancy of the patient at the time the patient begins treatment, which depends on the age of the patient. The values were estimated from Arias et al. (2008, Ref S3) Table 1 after rounding the age the patient begins treatment (i.e., (E) ((G),(H)) ) to the nearest integer value.
[e] Assumed to be equal to 1-average of the utility values for a non-fatal myocrdial infarction reported in Tsevat et al. (1993, Ref S6) (0.88 (0.84,0.93)), and Erickson et al. (2013, Ref S15) Table 1 (0.80 (0.50,0.90)).
[f] The loss duration is assumed to be equal to 1/2 the life expectancy of the patient at the time the patient begins treatment, which depends on the age of the patient. The values were estimated from Arias et al. (2008, Ref S3) Table 1 after rounding the age the patient begins treatment (i.e., (E) ((G),(H)) ) to the nearest integer value.
[g] =(B)x(I)x(L)x(O).
[h] =-SQRT( (((C)-(B))x(I)x(L)x(O))^2 + ((B)x((J)-(I))x(L)x(O))^2 + ((B)x(I)x((M)-(L))x(O))^2+((B)x(I)x(L)x((P)-(O)))^2 ), based on the assumption that the uncertainties in the terms are uncorrelated.
[i] =(R)+(S).
[j] =SQRT( (((D)-(B))x(I)x(L)x(O))^2 + ((B)x((K)-(I))x(L)x(O))^2 + ((B)x(I)x((N)-(L))x(O))^2+((B)x(I)x(L)x((Q)-(O)))^2 ), based on the assumption that the uncertainties in the terms are uncorrelated.
[k] =(R)+(U).
[l] Faish presentation (on behalf of the sponsor) to the FDA on 1995-09-28 (Ref S41, pp 114). Also Faish presentation to the FDA on 1995-11-16 (Ref S42, p 174).
[m] Assumed equal to minus the reduction in the Life expectancy in years relative to the baseline life expectancy in Arias et al. (2008, Ref S3) Table 1 if the annual probabiity of death between the age the treatment began (i.e., (E) ((G),(H)) ) and 109 years old is ((B)).
[n] =(T)-(R).
[o] =(V)-(R).
[p] Column total.
[q] =-SQRT(SUM((S)^2)), based on the assumption that the uncertainties in the estimated benefits for the adverse events prevented are uncorrelated.
[r] =SQRT(SUM((U)^2)), based on the assumption that the uncertainties in the estimated benefits for the adverse events prevented are uncorrelated.

### *Rezulin (troglitazone)*

This section describes the estimated risks and benefits of Rezulin based on information in Refs S57 through S68. The calculation steps and values are provided in Table S29 through Table S31 and the supporting sources and notes.

Rezulin (troglitazone) was originally approved in January 1997 (NDA 02-0720, Ref S60) for "patients with type II diabetes currently on insulin therapy whose hyperglycemia is inadequately controlled (HbA1c >8.5%) despite insulin therapy of over 30 units per day given as multiple Injections. ..." (Ref S61, PDF page 38). The risks of Rezulin at the time of approval were estimated to be **14.0 (1.7, 50.6)** deaths per 100,000 patient-years based on two cases with 'reversible jaundice' observed in the clinical studies, and the assumption that 1 in 10 of the 'reversible jaundice' cases would result in death (see Table S29). The benefits of Rezulin at the time of approval were estimated to be **329.5 (216.0, 442.9)** deaths prevented per 100,000 patient-years based on the percentage of patients in clinical studies that had "an HbA1C value below 8% at the end of the study," as indicated in the original approved package insert; 1996 DCCS data; and 1996 UK PDS data (see Table S30). The resulting risk/benefit ratio is 0.04257[3].

The FDA requested the manufacturers voluntarily withdraw Rezulin from the US market in March 2000 (HHS, 2000, Ref S65) based on liver failure onset reporting rates in post-marking data that were higher (e.g., **5.4 (1.7, 9.1)** more reported liver failure onsets per million

[3] The drug sponsor estimated the risk/benefit ratio to be 0.02 in March 1999 based on post-marketing data and updated efficacy data. This estimate however did not account for possible underreporting of deaths in the post-marketing data. The FDA decided to continue marketing Rezulin in March 1999 (i.e., no action), but began a priority review for the eventual approval of Avandia (rosiglitazone) and (Actos) (pioglitazone).

prescriptions) than alternative treatments (e.g., rosiglitazone and pioglitazone) (see Table S31). The benefits of Rezulin were assumed by the FDA to be the same as Avandia (rosiglitazone) and (Actos) (pioglitazone) (Lumpkin, 2000, Ref S66, Slide 41), so the incremental benefit of Rezulin is **0.0**. The FDA therefore concluded that Rezulin was an "out moded" drug (Lumpkin, 2000, Ref S66, Slide 43-44). The approval of Rezulin was formally withdrawn in August 2003 (68 FR 47581, Ref S68).

Table S29. Estimated Risk of Rezulin (troglitazone) corresponding to the FDA decision to approve NDA 20-720 on 1997-01-29.

| | (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) | (I) | (J) | (K) | (L) | (M) | (N) | (O) | (P) | (Q) | (R) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Serious Adverse Event | Controlled Clinical Trials | | | | | | | | | | Estimated Probability of Death/ Event | Estimated Risk | | | | | |
| | | Troglitazone | | | | | Placebo | | | | | | Deaths per Patient | | | Deaths per Patient-Year | | |
| | | Exposure | | Number of Events | Events/ Patient | Events/ Patient-Year | Exposure | | Number of Events | Events/ Patient | Events/ Patient-Year | | | | | | | |
| | | Patients | Patient-Years | | | | Patients | Patient-Years | | | | | | | | | | |
| | | PE | PE | PE | PE =(D)/(B) | PE =(D)/(C) | PE | PE | PE | PE =(I)/(G) | PE =(I)/(H) | PE | PE =((E)-(J))x(L) | LB | UB | PE =((F)-(K))x(L) | LB | UB |
| (1) | ALT > 3x upper limit of normal | 2510 [b,c,d,e] | 1426 [e] | 48 [b,c,d] | 1.9% [b,c,d] | 0.033661 | 475 [b,c,d] | 269.9 [f] | 3 [b,c,d] | 0.6% [b,c,d] | 0.011117 | | | | | | | |
| (2) | - withdrawn from the clinical study | 2510 [a,c,d,e] | 1426 [e] | 20 [a,c,d] | 0.8% [a,c,d] | 0.014025 | 492 [a,c,d] | 279.5 [f] | 0 [a,c] | 0.0% | 0.000000 | | | | | | | |
| (3) | - reversible jaundice | 2510 [a,c,d,e] | 1426 [e] | 2 [a,c,d] | 0.1% | 0.001403 | 492 [a,c,d] | 279.5 [f] | 0 | 0.0% | 0.000000 | 0.1 [i] | 0.000080 | 0.000010 [j] | 0.000288 [j] | 0.000140 | 0.000017 [k] | 0.000506 [k] |
| (4) | - no jaundice | 2510 [a,c,d,e] | 1426 [e] | 18 [g] | 0.7% | 0.012623 | 492 [a,c,d] | 279.5 [f] | 0 [g] | 0.0% | 0.000000 | | | | | | | |
| (5) | - not withdrawn from the clinical study | 2510 [a,c,d,e] | 1426 [e] | 28 [h] | 1.1% | 0.019635 | 492 [a,c,d] | 279.5 [f] | 3 [h] | | 0.010733 | | | | | | | |
| | Total | | | | | | | | | | | | 0.000080 | 0.000010 | 0.000288 | **0.000140** | **0.000017** | **0.000506** |

Sources and Notes:

PE Point Estimate

LB Lower bounds

UB Upper Bounds

[a] Approved Final Printed Labeling package insert (Ref S61, PDF page 38). Note the package insert (#0352G041, January 1997) in Ref S61 was submitted to the FDA on January 31, 1997 in NDA 20-720/S001. A comparison between the original approved package insert and the package insert on PDF pages 36-39 is located on PDF pages 69-70.

[b] NDA 20-720/S06 (Ref S61) p 109 (letter dated 1997-11-18, refers to all clinical studies in North America.)

[c] Watkins and Witcomb (1998, Ref S62).

[d] Parke-Davis (1999, Ref S64) pp 9-10.

[e] Graham presentation to the Endocrinologic and Metabolic Drugs Advisory Committee #72, in FDA documents (1999, Ref S63, PDF page 45).

[f] =(C)x(G)/(B), assuming that the placebo patients have the same treatment duration on average as the troglitazone patients.

[g] =(2)-(3).

[h] =(1)-(2).

[i] According to Parke-Davis (1999, Ref S64, p 16), 'hepatologists generally expect a minimum of 10 or more jaundice cases to every liver drug-associated death.'

[j] Calculated assuming that the probabity of a reported SAE per patient has a Binomial distribution using the MATLAB binofit((D),(B)) function (Ref S1), and assuming that the risk for the Placebo is zero. The confidence interval was then multplied by (L).

[k] Calculated assuming that the probabity of a reported SAE per patient has a Binomial distribution using the MATLAB binofit((D),(C)) function (Ref S1), and assuming that the risk for the Placebo is zero. The confidence interval was then multplied by (L).

Table S30. Estimated Benefit of Rezulin (troglitazone) corresponding to the FDA decision to approve NDA 20-720 on 1997-01-29.

| (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) | (I) | (J) | (K) | (L) | (M) | (N) | (O) | (P) | (Q) | (R) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Serious Adverse Event Prevented | Controlled Clinical Trials | | | | | | | | | | Estimated Effectiveness (Net percent reduction in cases due to Treatment) | | | | Estimated Prevented Rate (Events prevented per person-year) | | |
| | Estimated Absolute Risk without Metformin or Troglitazone (Events/person-year) | | | Treatment | Number of Patients | | Estimated Reduction | Control (e.g., Placebo) Number of Patients | | Estimated Reduction | | | | | | | |
| | PE | LB | UB | | | with HbA1c<8% | PE =(G)/(F) | | with HbA1c<8% | PE =(J)/(I) | PE =(H)-(K) | SE [g] | LB [h] =(L)-1.96x(M) | UB [h] =(L)+1.96x(M) | PE =(B)x(L) | LB =(B)x(N) | UB =(B)x(O) |
| Death | 0.010132 [a] | | | Metformin | 566 [b] | 212 [b] | 37.5% [b] | 354 [b] | 60 [b] | 16.9% [b] | 20.5% [b,f] | 2.8% [g] | 13.2% [i] | 27.8% [i] | 0.002078 | 0.001334 | 0.002821 |
| Death | 0.010132 [a] | | | Troglitazone (200 mg) | 116 [c] | 35 [e] | 30% [c] | 118 [c] | 13 [e] | 11% [c] | 19.2% [f] | 5.1% [g] | 5.9% | 32.4% | 0.001941 | 0.000598 | 0.003284 |
| Death | 0.010132 [a] | | | Troglitazone (600 mg) | 116 [c] | 66 [e] | 57% [c] | 118 [c] | 13 [e] | 11% [c] | 45.9% [f] | 5.4% [g] | 31.9% | 59.9% | 0.004648 | 0.003232 | 0.006065 |
| Death | 0.010132 [a] | | | Troglitazone (all) | 232 [d] | 101 [d] | 44% [c] | 118 [c] | 13 [e] | 11% [c] | 32.5% [f] | 4.3% [g] | 21.3% | 43.7% | **0.003295** | **0.002160** | **0.004429** |

Sources and Notes:

LB Lower bounds of the estimate

PE Point estimate

SE Standard error of the point estimate

UB Upper bounds of the estimate

[a] Based on results in Table 2 of Turner et al. (1996, Ref S59), which indicate that 7.7% of patients with non-insulin-dependent diabetes mellitus had fatal diabetes related endpoints over a median exposure of 7.6 years. These results are based on both conventional and intensive therapies, and therefore the value may underestimate the risk for conventional therapy.

[b] NDA 20-357 (Ref S58) Medical Officer Review, p 9 (PDF page 11). Estimated reduction in HbA1c to less than 7%.

[c] Approved Final Printed Labeling package insert (Ref S61, PDF page 36). Note the package insert (#0352G041, January 1997) in Ref S61 was submitted to the FDA on January 31, 1997 in NDA 20-720/S001. A comparison between the original approved package insert and the package insert on PDF pages 36-39 is located on PDF pages 69-70.

[d] =sum of 200 mg and 600 mg doses.

[e] =number of patients N x the percentage reduction in NDA 20-720 Final Printed Labeling (Ref S61, PDF page 36), rounded to the nearest integer.

[f] NDA 20-357 (Ref S58) Medical Officer Review, pp 9-10 (PDF pages 11-12) assumed 'that a HbA1c of less than 7% may not associate with microangiopathy', and therefore not at risk of death due to ESRD, based on the data in Figure 5A of DCCT (1993, Ref S57). The DCCT data in Figure 5A also indicates that that HbA1 of less than 8% may also not associate with microangiopathy.

[g] =SQRT( (H)x(1-(H))/(F) + (K)x(1-(K))/(I) ) according to Eqn (2.13) in Fleiss (1981, Ref S2).

[h] 95% confidence interval according to Eqn (7.6) in Fleiss (1981, Ref S2).

[i] The result in NDA 20-357 (Ref S58) Medical Officer Review, p 9 (PDF page 11) is the 99% confidence interval, which is equal to (L) ± 2.576x(M).

Table S31. Estimated Risk of Rizulin (troglitazone) corresponding to the FDA decision to request market withdrawal on 2000-03-21.

| | (A) | (B) | (C) | (D) | (E) | (F) | (G) | (H) | (I) | (J) | (K) | (L) | (M) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Drug | Post Marketing Data | | | | | | | | | | | |
| | | Marketing Period | Exposure | | Reported Liver Failure Onset | Reporting Rate | | | | | | | |
| | | | Prescriptions | Patients | | Per Prescription | | | | Per Patient | | | |
| | | | PE | PE | PE | PE =(E)/(C) | SE | LB =(F)-1.96x(G) | UB =(F)+1.96x(G) | PE =(E)/(D) | SE | LB =(J)-1.96x(K) | UB =(J)+1.96x(K) |
| (1) | Troglitazone | 1st 3 quarters after launch [a] | 2,402,000 [b] | 800,000 [b] | 16 [b] | 0.0000067 | 0.0000017 [d] | 0.0000034 | 0.0000099 | 0.0000200 | 0.0000050 [e] | 0.0000102 | 0.0000298 |
| (2) | Rosiglitazone | 1st 3 quarters after launch [a] | 1,563,000 [c] | 500,000 [c] | 2 [c] | 0.0000013 | 0.0000009 [d] | -0.0000005 | 0.0000031 | 0.0000040 | 0.0000028 [e] | -0.0000015 | 0.0000095 |
| (3) | Change | | | | | **0.0000054** [f] | 0.0000019 [g] | **0.0000017** | **0.0000091** | **0.0000160** [f] | 0.0000057 [g] | **0.0000047** | **0.0000273** |

Sources and Notes:

LB Lower bounds of the estimate

PE Point estimate

SE Standard error of the point estimate

UB Upper bounds of the estimate

[a] Lumpkin stated in Ref S67 page 73 (PDF page 77) that 'the launch versus launch was a more defensible comparison than the conteporaneous comparison.

[b] Lumpkin (2000, Ref S66) slide 16 and transcript (Ref S67) page 66.

[c] Lumpkin (2000, Ref S66) slide 17 and transcript (Ref S67) page 67.

[d] =SQRT((F)x(1-(F))/(C)) according to Eqn (1.23) in Fleiss (1981, Ref S2). Note that this is an approximation for binomial distributed data.

[e] =SQRT((J)x(1-(J))/(D)) according to Eqn (1.23) in Fleiss (1981, Ref S2). Note that this is an approximation for binomial distributed data.

[f] =(1)-(2)

[g] =SQRT((1)^2+(2)^2). See Eqn (2.13) in Fleiss (1981, Ref S2).

## Appendix C - Receiver Operator Characteristic (ROC) of the FDA Approval Model

The Receiver Operator Characteristic (ROC) curve for the FDA approval model is depicted by the solid blue curve in Figure S1. This curve shows the outcome sensitivity versus 1-specificity of the estimated FDA approval model as the probability criteria to classify the outcome "cut-point" varies from 0 to 1. The outcome sensitivity is the probability of correctly predicting the approval or withdrawal based on whether or not the predicted probability is greater than or less than a probability cut-point. One minus the specificity is the probability of incorrectly predicting the approval or withdrawal. The dotted black diagonal line represents the expected value for a model with no ability to discriminate between approvals and withdrawals (e.g., a coin toss) for comparison purposes. Sensitivity values greater than 1-specificity are desired.

The area under this ROC curve (AUC) is 0.952, which is statistically significantly greater than the area under the black diagonal curve (0.5). According to Hosmer and Lemeshow [S69], models with AUC values greater than 0.9 are considered to have outstanding discrimination.

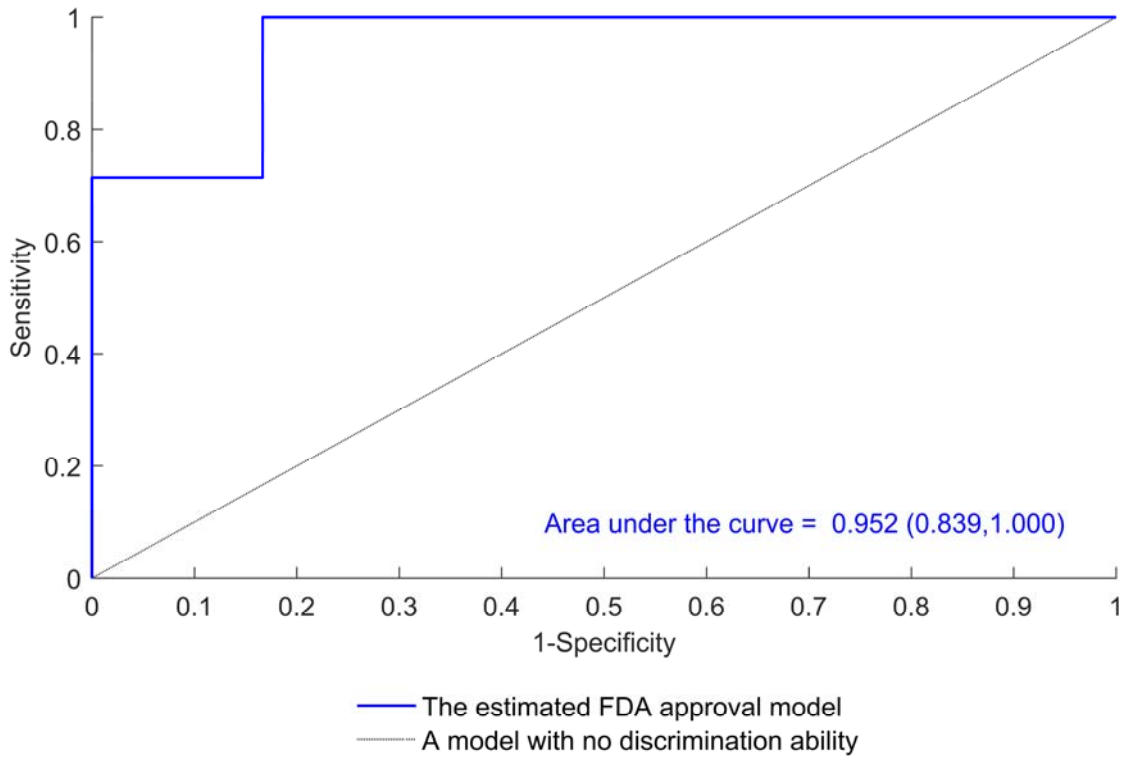



Figure S1. ROC Curve for the Probability of FDA Approval Model

## Appendix D - Estimated Model Sensitivity to the Assumed R/B Ratio if the Benefit is Zero

There were two FDA actions listed in Table 1 with the estimated benefit equal to zero. Therefore the Risk/Benefit ratio for these actions is mathematically undefined. The Risk/Benefit ratio approaches positive infinity as the positive benefit value approaches 0 (provided that the risk is a positive value). It was assumed for the purpose of the main logistic regression analysis that the risk/benefit ratios for these two FDA actions were 100, as indicated in Table 2. The assumed value of 100 was chosen because a) it was larger than all of the other Risk/Benefit ratios in Table 2; and b) small enough so the domain of all Risk/Benefit was relatively balanced on the horizontal log scale shown in Figure 1.

The sensitivity of the estimated FDA approval model to this assumed Risk/Benefit value when the benefit is 0 was investigated by re-estimating the model coefficients using different assumed Risk/Benefit values. Four separate models were estimated using assumed Risk/Benefit values of 10, 100, 1000, and 10000 respectively. The second model is identical to the model reported in the main paper. We also re-estimated the model coefficients excluding the two observations with zero estimated benefit.

The results of this sensitivity analysis are illustrated in Figure S2. Figure S2 is similar to Figure 1 in the main paper with the following exceptions: a) the fixed Risk/Benefit ratio data are depicted with filled triangles, and the variable Risk/Benefit ratio data are depicted with open triangles; b) there are five solid blue curves, one for each estimated model; and c) the 95% profile likelihood confidence intervals for each model have been added. The confidence intervals are depicted by doted curves.

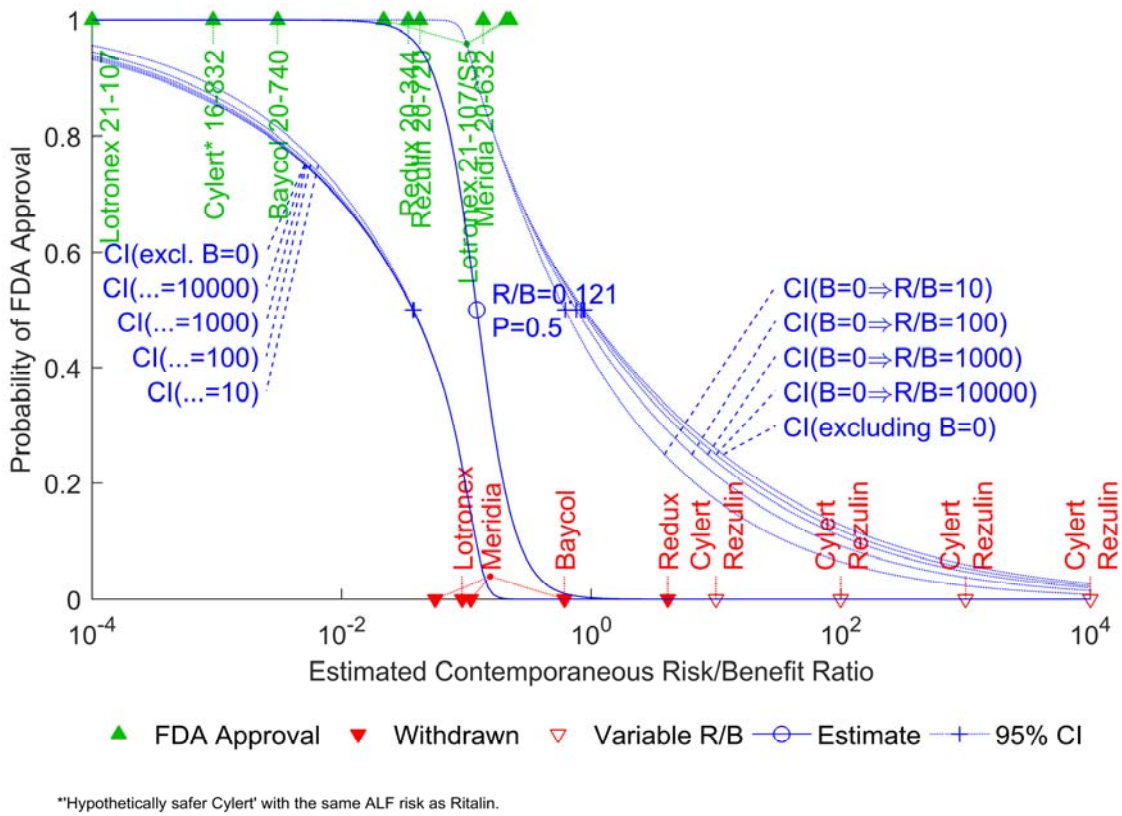
The five solid blue curves in Figure S2 are nearly identical and indistinguishable from each other and the curve in Figure 1, indicating that the estimated model is relatively insensitive to the assumed Risk/Benefit ratios considered in this analysis. The variation in the estimated model coefficients was much less than the two significant figures reported in the main paper (i.e., all of the estimated values for $\beta_0$ and $\beta_1$ round to -5.97 and -2.83 respectively). The reason for this insensitivity is that estimated probability of FDA approval is close to zero for Risk/Benefit ratios greater than 1. Therefore the incremental deviance for these "withdrawn from market" observations are very small and as a result they have very little influence on the estimated values model coefficients (i.e., the point estimates).

The results in Figure S2 also indicate that the 95% confidence intervals for the estimated model are more sensitive to the assumed Risk/Benefit ratios. The estimated confidence intervals tend to approach the result for the model excluding the two observations, as the assumed Risk/Benefit ratio increases from 10. The size of the estimated confidence interval decreases when the assumed Risk/Benefit ratio is decreased towards 10. The reason for this is that the estimated probability of FDA approval evaluated at a Risk/Benefit ratio of 10 is more sensitive to the model coefficients than the probability evaluated at larger Risk/Benefit ratios (even though the actual difference between the model and data are very small). The profile confidence intervals for the model with the two observations removed are reported in the main paper because they provide a conservative estimate of the uncertainty in the model coefficients.

The ROC curve was found to be insensitive to the changes in the assumed Risk/Benefit ratios, but sensitive to excluding observations. The area under the ROC curve (AUC) decreases from 0.952 to 0.929 when the two observations with zero estimated benefit are excluded. This AUC

result is still statistically significantly greater than the area under the black diagonal curve (0.5) and still indicates outstanding discrimination.

In summary, the results of this sensitivity analysis indicate that: a) the estimated FDA approval model is insensitive to the assumed Risk/Benefit value of 100 when the benefit is zero; b) the ROC results indicates that using all of the observations are helpful in estimating and confirming the model, but c) the uncertainty in the model is conservatively estimated when the two observations with zero benefit are not used to estimate the confidence interval.




*'Hypothetically safer Cylert' with the same ALF risk as Ritalin.

Figure S2. Sensitivity of the Estimated Probability of FDA Drug Approval Model to Changes in the Assumed Risk/Benefit Ratio for Observations with Zero Estimated Benefit

## References for the Appendices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