



Panel Backs Approval of Contrave

Contrave and Qnexa Both On Track for FDA Approval

Drug name: **Contrave**
(naltrexone/bupropion)

Developer: **Orexigen (OREX)** and
Takeda

Probability of Approval: **87%(B)**,
increased from 72%(C)

Estimated Approval Date: **March 2011**

2017 Worldwide Revenue:
\$765 million

Drug name: **Qnexa**
(phentermine/topiramate)

Developer: **Vivus (VVUS)**

Probability of Approval: **71%(C)**

Estimated Approval Date:
August 2011

2017 Worldwide Revenue:
\$828 million

Drug name: **Lorcaserin**

Developer: **Arena (ARNA)** and **Eisai**

Probability of Approval: **43%(F)**

Estimated Approval Date: **August
2012**

2017 Worldwide Revenue:
\$646 million

- In a 13-7 vote, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee **recommended approval of Orexigen (OREX) and Takeda's Contrave** for obesity.
- The commitment to conduct a post-approval trial examining the cardiovascular risks associated with Contrave, and a well prepared risk-mitigation strategy may have tipped the scales in favor of the positive recommendation.
- For now, Contrave jumps to the head of the queue of obesity drug candidates vying for approval. We model a March 2011 approval for Contrave, now with an 87% probability of approval. If approved, we model \$765 million in worldwide sales by 2017.
- The positive FDA panel meeting does not change our outlook for the other two late-stage obesity drugs - Arena's (ARNA) and Eisai's lorcaserin and Vivus's (VVUS) Qnexa. Vivus has a much higher likelihood of approval than lorcaserin, while Contrave has moved into the pole position in the race to be the first obesity drug approved in the U.S. in over a decade.

Tuesday, Orexigen and Takeda faced the FDA's Endocrinologic and Metabolic Drugs Advisory Committee and accomplished what rivals Vivus and Arena have been unable to do: convince the panel that the weight-loss benefits seen with their drug outweighed concerns surrounding risks. Following the positive outcome of the panel, we review our models for Contrave, Qnexa, and lorcaserin. We highlight what went right for Contrave, the potential hurdles which still lay ahead, and the implications for Qnexa and lorcaserin.

What Went Right

Orexigen seems to have benefitted from observing the FDA advisory panel meetings for Qnexa and lorcaserin. Vivus made a mistake by not addressing Qnexa's weaknesses with mitigation strategies. This, coupled with the lack of long term data, were the main sticking points at the panel resulting in the issuance of a complete response letter. Arena failed to convince its panel that lorcaserin's modest therapeutic and clinical benefits offset the risks associated with the agent.

While Orexigen also lacked long-term Contrave data, the company outlined a solid risk management plan, were proactive in bringing Abbott's Meridia (sibutramine) into the discussion, and acknowledged that additional studies assessing cardiovascular risk would be needed to support continued marketing.

REMS

Reviewers zeroed in on five areas of safety: blood pressure and heart rate, cardiovascular events, seizures, psychiatric-related adverse events, and neurological/cognitive adverse events. The first three concerns dominated the discussion, with perhaps the most focus on the question of why Contrave appears to raise blood pressure in certain patients even while facilitating weight loss.

To address these concerns, Orexigen proposed a detailed risk management strategy (REMS; risk evaluation and mitigation strategy) for Contrave. While several ideas were presented, the sponsor primarily stressed that the evaluation of weight loss, blood pressure, and heart rate in the first four months of treatment could predict a patient's ultimate success and risk.

Orexigen suggested that the identification of early responders was critical to mitigating the cardiovascular risk associated with Contrave. Several analyses were conducted to evaluate whether earlier weight loss (weeks 4-28) was predictive of a 5% or greater weight loss response at the end of treatment (week 56). Based on receiver operating characteristic curves, 5% weight loss from baseline at week 16 showed 75 to 85% accuracy in the four phase III trials in identifying 5% responders at week 56. Moreover, in a pooled analysis of the four phase III trials, among the subjects treated with Contrave32 who achieved $\geq 5\%$ weight loss at week 56 based on last observation carried forward (LOCF), more than 85% reached the responder status by week 16.

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Orexigen proposed that by monitoring patients closely during the first four months, physicians could identify early responders. Those patients who demonstrate 5% weight loss in the first few months and do not show increases in blood pressure or heart rate would remain on therapy.

Orexigen also addressed its approach to mitigating increased blood pressure and heart rate. Using odds ratio based on logistic regression, Orexigen scientists presented analyses demonstrating that those patients who were considered systolic blood pressure outliers early in treatment (weeks 4-16) had at least 12 times the odds of having outlier values later in treatment. Similar findings were noted for diastolic blood pressure and heart rate.

While these proposed risk mitigation strategies may have tilted the balance in favor of approval, we warn that Orexigen's proposed strategy, no matter how detailed, may not yield optimal real-world risk reduction. A posthoc analysis of sibutramine's SCOUT trial did not provide convincing evidence that changes in heart rate and blood pressure resulting from sibutramine accurately predicted the excess adverse cardiovascular events eventually observed.

Although suicidality and seizures were of secondary concern to the panel, Orexigen suggested following the approach of bupropion's risk mitigation strategy for these events.

CV Study

Orexigen won over several panelists by insisting a cardiovascular safety study was the only way forward. Details on trial design were limited, but Orexigen argued such a study could only be done in the post-approval setting. One panelist agreed, stating that it was only in the post-approval setting that a trial could enroll the required 10,000 patients and number of events to identify the agent's cardiovascular risk.

Panelists voted 11 to 8, with one abstention, that the FDA require Orexigen to conduct a study to examine Contrave's effect on risk for major adverse cardiac events after the agent's approval and not before, citing concerns that requiring a cardiovascular outcomes study prior to approval would essentially kill the program.

Several panelists remained unconvinced that Contrave should be approved without such a study. This sentiment can be summed up by Sanjay Kaul, the Director of the Vascular Physiology and Thrombosis Research Laboratory at the Burns and Allen Research Institute at Cedars-Sinai Medical Center, "The more I look into it, the more I conclude that this drug resembles sibutramine both in terms of efficacy and cardiometabolic profile, blood pressure, and heart-rate signals. There is an opportunity to learn from history, or we are likely to repeat it."

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Other Issues

Although panel members were disappointed in the magnitude of weight loss seen across the phase III program, the majority concluded that the agent satisfied the FDA's criteria for approval. Michael Rogawski, a neurologist at the University of California Davis commented, "I feel the sponsor met the requirements of the FDA.... On the other hand, I feel this is a very flawed product."

The briefing documents noted that it was difficult to draw accurate conclusions about the long-term efficacy of Contrave given that some subjects were re-randomized prior to week 56 in study NB-303. Although the issue did not dominate the panel's

discussion, several panel members, including Dr. Kaul and Dr. William Hiatt, Professor of Cardiovascular Research at the University of Colorado Denver, suggested that efficacy may have in fact have been overstated as a result of the re-randomization design incorporated into the trial.

Panel members also noted that the exclusion criteria for Orexigen trials were so broad that the treated patients might not reflect real-world use of the drug.

Implications for Qnexa and Lorcaserin

The positive recommendation, based on only one year of data, bodes well for Vivus's Qnexa. Qnexa has demonstrated approximately double the weight loss of Contrave, and we anticipate that the two-year safety data from the 1,000 patient SEQUEL extension study is likely to satisfy the FDA on the issue of long-term safety. The *inThought* Approvability Index for Qnexa remains unchanged at 71%(C). We continue to project \$828 million in worldwide sales by 2017 and estimate an August 2011 approval.

Our outlook for Arena and Eisai's lorcaserin is considerably less optimistic. Lorcaserin's advisory panel concluded that that the drug's marginal efficacy does not offset even modest safety concerns, implying that Arena and Eisai may never be able to generate enough satisfactory data to gain approval. The most likely path forward for lorcaserin is riddled with the risk inherent in a new phase III trial program. While lorcaserin monotherapy is unlikely to yield different results in new trials, sponsors could conduct trials of lorcaserin in combination with other agents, such as phentermine or a glp-1 analog in an effort to demonstrate better efficacy. Eisai could bring the necessary resources to the table, but this strategy would delay approval of lorcaserin for several years. The IAI score for lorcaserin remains 43%(F). If approved, we project 2017 worldwide sales of \$646 million, and continue to model approval in August 2012.

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