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SPOTLIGHT ON... OBESITY

A PHARMA MATTERS REPORT.

OCTOBER-DECEMBER 2010

Expert therapy area review of the key market players and deals highlights for leading areas of industry investment and development. These insightful reviews are based on the strategic data and insights from *Thomson Reuters Pharma*[™] and *Thomson Reuters Forecast*[™].



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ABSTRACT

Tapping into the obesity market has become one of the greatest challenges of the pharmaceutical industry. Obesity is a global epidemic and, together with its associated diseases of type 2 diabetes and cardiovascular disease, is set to become one of the greatest healthcare burdens affecting society. Given the sheer numbers of patients needing treatment, obesity should be a multi-billion dollar revenue earner, but *Thomson Reuters Forecast* indicates that the market is shrinking, due to challenges in developing agents with an acceptable risk/benefit profile. This review discusses the problems besetting the pharmaceutical industry, as key products are withdrawn from the market, and reveals the potential major players that could turn the market around. The fluidity of the current market outlook means that the deals landscape has also transformed through necessity. Covered by this article is an in-depth critique of licensing, as companies strive to invest in the potentially profitable obesity drugs of the future.

SECTION I

OBESITY: A 21ST CENTURY EPIDEMIC

Obesity is the global epidemic of the 21st century. The CDC has declared it to be the number one health threat in the US. At the present time, worldwide there are over 1 billion adults who are overweight, with 300 million classed as clinically obese. By 2015, the World Health Organization predicts this figure to rise to 2.3 billion overweight and 700 million clinically obese. Industrialized societies are not the only regions affected, with rates of obesity often rising faster in developing countries.

The contributing factors to obesity are multifaceted and complex. Economic growth, modernization and globalization of food markets are key factors, as are changes in societies, as populations become more affluent and urbanized. In recent decades, there has been a general shift in society to a more sedentary lifestyle and increased consumption of nutrient-deficient foods containing high levels of saturated fats and sugars. Obesity affects all populations, though most alarming to clinicians is the escalation in childhood obesity.

Healthcare professionals are keen to tackle obesity as it is the primary risk factor for developing a plethora of debilitating and life-threatening diseases, including type 2 diabetes, cardiovascular diseases, including hyperlipidemia and hypertension, stroke, and certain types of cancer. Obesity increases the risk of premature death and contributes to serious, chronic conditions that reduce overall quality of life, including gall bladder, respiratory and degenerative joint diseases. The healthcare burden of obesity and its associated morbidities is therefore immense. In the US alone the estimated cost of treating obesity-associated disease is \$90 billion per year. With such mammoth costs involved, global governments are eager to address this escalating economic burden and to endorse viable treatment solutions. These cost factors, twinned with the vast numbers of potential patients and the huge unmet medical need, makes obesity potentially one of the most lucrative target markets for the pharmaceutical industry.

DIVERSE TREATMENT OPTIONS, BUT PHARMACEUTICAL INTERVENTIONS HAVE FALLEN SHORT

Treatment of obesity is multifarious, with initial approaches based on improved diets and patients increasing levels of physical activity. While lifestyle changes are effective, many patients struggle to comply with challenging fitness and diet regimes. Maintaining the lifestyle that led to weight loss is an even greater challenge. Surgical procedures are becoming more popular and represent an effective treatment option for severely obese patients who have had no success with other interventions, but are associated with usual surgical risks, long-term digestive problems, and mineral and vitamin deficiencies. The holy grail of obesity treatment would be a simple pill that induces substantial (>10%) long-term weight loss.

Studies of the diverse mechanisms controlling weight regulation have brought to the table several pharmaceutical treatment options for obesity. Historical therapeutics were short term agents, to be used to 'kick-start' a weight loss regime. Redux (dexfenfluramine) was the only long-term treatment option until its withdrawal in 1997 due to reports of valvulopathy just a year after launching.

Safety issues and abuse potential have long plagued obesity drugs. Most of the early obesity drugs launched in the '50s and '60s were amphetamine derivatives, with addictive properties, thus only approved for short term use.

Global trend in obesity offers tremendous growth opportunity; according to the WHO, approximately 1.6 billion adults are overweight, and by 2015, this number is projected to rise to 2.3 billion, with over 700 million classified as obese.

These included Preludin (phenmetrazine) or Bondril (phendimetrazine), and phentermine, launched in 1959, generic versions of which, in spite of its addictive and stimulant properties, remain the number one obesity therapy by volume due to low cost. Fenfluramine, a short-term 5-HT stimulator agent that increases the feeling of fullness and causes a loss of appetite, had an advantage over the amphetamine derivatives as there was less potential for abuse, however, it was withdrawn at the same time as the other drug in its class, Redux, also due to valvulopathy.

Given the historical issues with weight loss products, the challenge for the pharmaceutical industry is to develop an agent that promotes long-term weight loss, is effective in the majority of patients, is safe for long-term use and that has no addictive side effects. Despite guidelines for applications for new obesity agents being redrafted in the US in 1996 to address these issues, three out of four of the next-generation products launched since the guidelines were published have been withdrawn due to serious side effects. Redux withdrawal in 1997 was followed by Acomplia (rimonabant) in January 2009 and, most recently, Meridia (Reductil; sibutramine), withdrawn in October 2010. At the time of this article going to press, Orlistat remains the only obesity agent licensed for long-term use in global markets. A market that should in theory be growing is in fact diminishing in terms of revenue and products.

ACOMPLIA LINKED TO DEPRESSION AND SUICIDAL THOUGHTS

The first-in-class cannabinoid (CB1) antagonist Acomplia (sanofi-aventis) was launched in 2006. Sanofi-aventis maintained that the drug was well received on launch in the EU, but it only managed to rack up total revenue of €79 million in 2007, its first full year of sales.

The unique selling point of Acomplia was that, as well as reducing weight and waist circumference, it improved HDL-C and triglycerides, and glycemic control. The product targeted the triumvirate of diseases that are the biggest healthcare concern in developed markets: obesity, cardiovascular disease and type 2 diabetes. However, these clinical attributes were not enough to save the drug from the axe. The FDA unanimously voted not to approve Acomplia for obesity in 2007 due to increased risk of psychiatric disorders. The EU then removed its marketing authorization for Acomplia in January 2009, after an analysis of pooled data revealed that the risk of psychiatric disorders, including depression and suicidal thoughts, doubled with Acomplia use.

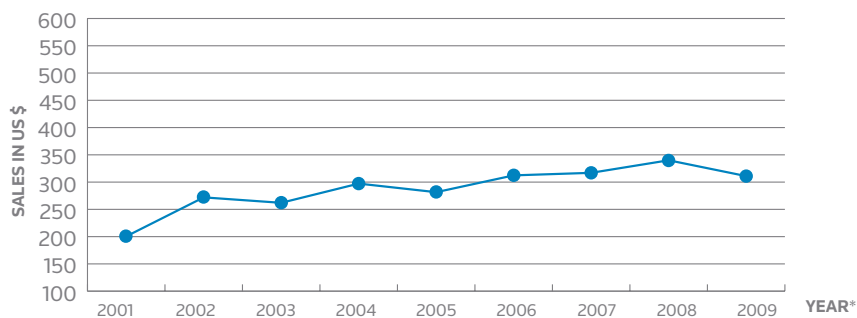
MERIDIA WITHDRAWN DUE TO INCREASING CARDIOVASCULAR RISK

Abbott Laboratories' norepinephrine and 5-HT uptake inhibitor Meridia (Reductil) was withdrawn in October 2010, after almost twelve and a half years on the market. As a nonamphetamine appetite suppressant, side effects were primarily mild and temporary. However, people taking Meridia also displayed substantial increases in blood pressure that required monitoring. At launch, the drug was not recommended for use in patients with existing hypertension. Also, due to being centrally acting, the product has always been classified as a schedule IV drug. Meridia sales had peaked at \$340 million by 2008.

Despite sustained efficacy in weight loss (of 5 to 10%), cardiovascular safety concerns surrounding the drug were not to be swept under the carpet. In 2002, a Public Citizen's petition was lodged with the FDA requesting the drug to be banned, due to filing data reporting significant increases in blood pressure and heart rate, key risk factors for heart attacks.

The FDA denied the petition and it was not until after publication of SCOUT data in late 2009 that it issued advice that the drug should not be used in patients with a history of cardiovascular disease. SCOUT showed Meridia significantly increased the number of patients with heart attacks, strokes, resuscitated cardiac arrests or deaths in obese patients with known or occult cardiovascular disease. The EU initially took more extreme measures than the FDA, suspending Meridia's license in January 2010. However, by October 2010, the FDA also requested that Abbott withdraw the drug. Other markets in North America and Australasia have since followed suit, although Eisai has yet to withdraw its application for obesity in Japan, filed in November 2007. The product is still available in some markets, such as South Korea, Mexico and South America, and Abbott still strongly believes that Meridia has a positive risk/benefit profile in its approved patient population.

MERIDIA: REPORTED REVENUE (MILLION US\$)



* Data are derived from Thomson Reuters Forecast

XENICAL 'SAFE' BUT REVENUE CANNIBALIZED BY OTC ALLI

With Meridia's withdrawal, the only obesity agent licensed in worldwide markets for long-term use is Xenical (orlistat), Roche's inhibitor of intestinal lipases. The drug has been available in the US and EU since 1999. Xenical is non-systemic thus displays minimal systemic side effects. It has an added advantage in that since 2004 it has been approved for use in obese adolescents, a patient population that is increasing in prevalence worldwide. Obesity in children is of increasing concern to clinicians, not least because overweight children tend to become overweight adults.

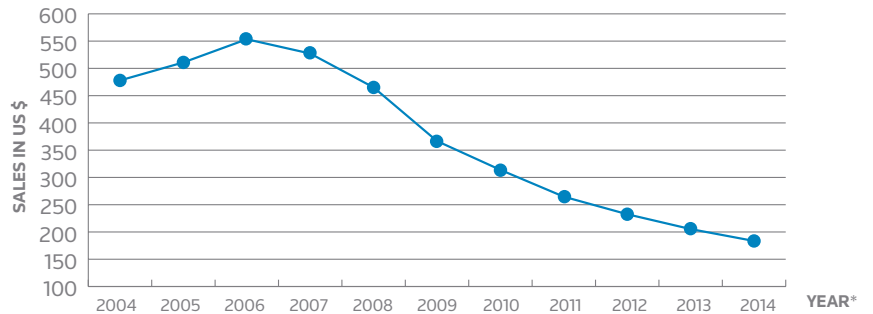
Lack of reimbursement for anti-obesity pharmacotherapy may limit market growth. For example, in Germany, Xenical is classified as a lifestyle drug.

Xenical is one of the first pharmaceutical agents to obtain a label extension for reducing the risk of development of type 2 diabetes, based on the landmark XENDOS study. The impaired glucose tolerance market is one that has been targeted by big pharma for many years. Type 2 diabetes is a key comorbidity with obesity and so this label amendment has significantly strengthened the product in the obesity franchise. Clinical studies have also shown improvement in lipid profiles and blood pressure reductions, suggesting that Xenical may reduce cardiovascular risk in obese patients, another key comorbidity.

Despite Xenical's strength of label and apparent clinical benefits (sustained weight loss benefits of between 5 and 10%), the product is not effective in all patients. Its use is also associated with unpleasant gastro-intestinal (GI) side effects which patients can be intolerant to, including oily spotting, flatus with discharge, and fecal urgency. To limit these GI side effects, patients have to reduce fat intake and spread it evenly over meals. The drug also has to be administered three times a day and patients must take vitamins to reduce the likelihood of vitamin starvation from excretion of nutrients due to Xenical use. These are inconveniences that require lifestyle changes and reduce patient compliance, which in turn reduces product efficacy and raises the spectre of risk/benefit profile for this product also.

Tolerability issues have likely capped Xenical's sales. Following a rapid ramping up of sales immediately following launch, sales held steady at around \$500 million until 2006. Since 2007, sales have been diminishing. At this time, an OTC version of the product was launched, Alli, which has cannibalized sales. Xenical lost its patent exclusivity in December 2009, which will severely impact revenue going forward.

XENICAL: REPORTED AND CONSENSUS FORECAST REVENUE (MILLION US\$)



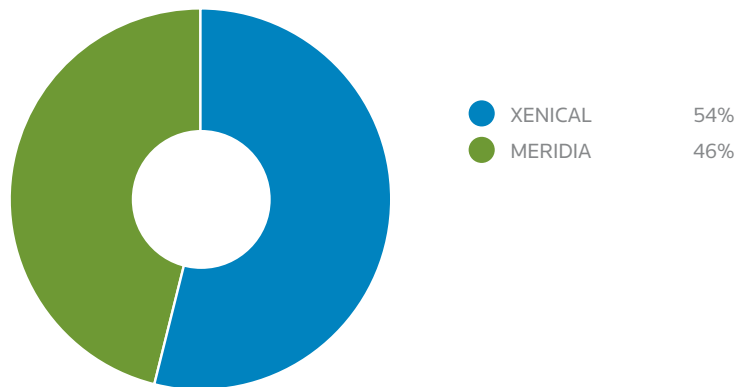
* Data are derived from Thomson Reuters Forecast

REVENUE POTENTIAL OF THE OBESITY MARKET IS UNREALISED SO FAR

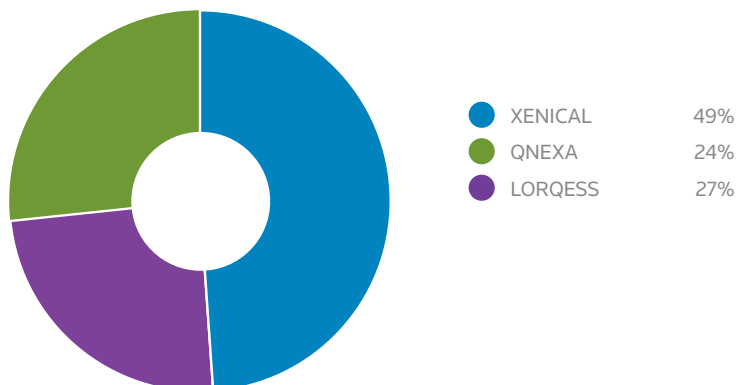
None of the above next-generation products have been able to tap into the revenue potential of the obesity market. Most have been held back by safety issues and concerns that the risks of use outweigh the benefits. *Thomson Reuters Forecast* data show that what could have been a multi-billion dollar revenue market for the pharmaceutical industry has been restricted to a mere \$677 million in 2009. At this time Xenical was the market leader in revenue terms with 54% market share and reported sales of \$366.7 million. Prior to its withdrawal in key regional markets, Meridia held the remaining 46% market share and earned only \$311 million in 2009.

Increased emphasis of lifestyle modification such as diet and physical exercise are still the recommended treatment modalities.

OBESITY WORLDWIDE (US\$) 2009 REPORTED SALES



OBESITY WORLDWIDE (US\$) 2014 CONSENSUS FORECASTS



The recent raft of withdrawals in the market means that the obesity landscape of 2014 looks very different to the market dynamics model observed in 2009, both in terms of products and revenue. At the present time, the industry seems to be racking up failures, as promising drugs fail to jump stringent regulatory hurdles and are held at the starting line. VIVUS's Qnexa (a combination of low-dose phentermine and topiramate) was surprisingly not recommended for US approval in July 2010. In October 2010 another promising agent, Lorqess (Arena Pharmaceutical's lorcaserin), was turned down by the FDA. Orexigen's Contrave, a combination of bupropion and naltrexone, is the only late stage product specifically developed for obesity still in the running for US approval. As these products limp through the regulatory process, revenue in the obesity market is forecast to decrease by half to \$375.3 million by 2014, according to *Thomson Reuters Forecast* data.

LORQESS DENIED APPROVAL BY FDA

Arena Pharmaceutical's selective 5-HT_{2c} receptor agonist Lorqess (lorcaserin) was denied approval by the FDA in October 2010 apparently due to its weak risk/benefit profile. Data submitted in the NDA from the BLOOM and BLOSSOM trials showed Lorqess induced only marginal weight loss (a placebo adjusted average weight loss of only 3.6%) and preclinical studies revealed a concerning potential for increased risk of breast cancer and astrocytoma at relatively low doses.

These objections are not yet insurmountable. The FDA has requested data from the BLOOM-DM one-year extension trial, now complete. These data may satisfy the authorities on efficacy. Alleviating concerns of tumorigenicity may prove to be more difficult, given that the patient population to be treated already has an elevated risk of breast cancer. Centrally-acting Lorqess is also likely to carry a Schedule IV of the Controlled Substance Act, if approved, a common occurrence with short term agents, but which may impede its utility in long-term use.

An upside to these drawbacks exists. Although Lorqess's weight loss efficacy is modest, it is in-line with Xenical and Meridia. And it has a relatively impressive side effect profile compared with others in the obesity franchise. Trials have shown no increased risk of depression or suicidal thoughts. Its cardiovascular safety also appears robust. The high selectivity of Lorqess means that it has little effect on cardiovascular channels, one of the key reasons for withdrawal of its 5-HT predecessors, such as fenfluramine. And as yet, there have been no reports of valvulopathy. It has improved cardiovascular safety to Meridia, which elevates blood pressure, and is better tolerated than Xenical, with its GI side effects.

Tolerability may become Lorqess's unique selling point, if the product is approved, making it ideally suited to the mildly obese patient dynamic. It is also ideally positioned to slip into the void created by Meridia, though modest efficacy may restrict its wider adoption. *Thomson Reuters Forecast* indicate the drug could garner revenue of \$445.1 million by 2020.

Wider acceptance and growing use of bariatric surgery and other invasive procedures to engender profound weight loss, may limit use of anti-obesity drugs.

QNEXA FAILURE TO GAIN APPROVAL RECOMMENDATION IN THE US A SURPRISE

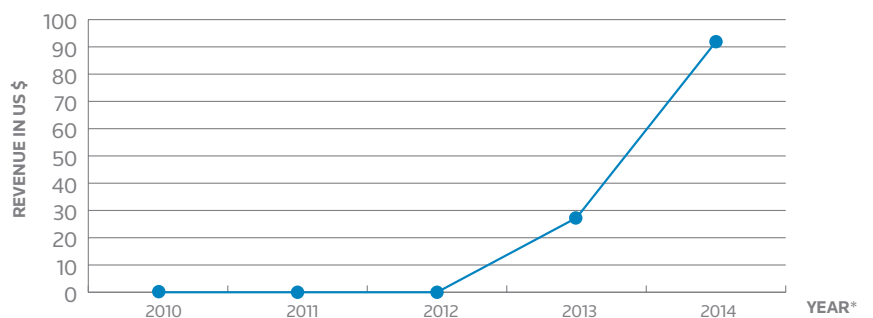
Many in the industry were surprised when an FDA advisory panel did not recommend for approval VIVUS's phentermine and topiramate combination Qnexa, given that the individual agents have been used to treat obesity for a number of years. Safety data identified increased risks of depression, memory loss and metabolic acidosis, and increased heart rate, but of key concern to the panel was potential teratogenicity due to the topiramate component and the lack of cardiovascular safety data.

Efficacy data for Qnexa is strong, with many clinicians viewing its weight loss data as the most robust for any obesity agent. EQUIP and CONQUER trials found 11% and 10.4% weight loss for a full dose of Qnexa, respectively in the ITT population, significantly above the FDA required benchmark of 5%. A high number of patients also responded to therapy. In the CONQUER trial, 70% of patients in the ITT population lost > 5% weight. Weight loss was also sustained, with the one year extension study SEQUEL demonstrating patients achieving a two-year average weight loss of 11.4% on high-dose Qnexa. Additional attributes of the product are improvements in metabolic and lipid profiles, hinting at utility in the co-morbidities type 2 diabetes and cardiovascular disease.

The PDUFA date for Qnexa was October 28, 2010. At this time the FDA stated it could not approve Qnexa in its present form. VIVUS was hoping to address the FDA's labelling and safety questions before the PDUFA date and planned to conduct a post-approval cardiovascular outcomes study with 8,000 to 10,000 'at-risk' patients. Analysts felt this was unlikely to placate the FDA and if it withheld approval until these trials are completed, there could be at least a three to four year delay in the product reaching the market. Teratogenicity could, however, prove to be an insurmountable weakness, especially considering that women aged 20 to 44 years is the population demographic that is most likely to be seeking weight loss treatment. The October response, however, was that VIVUS needs to provide a comprehensive assessment on how the company will evaluate and mitigate teratogenic potential in women of childbearing age, and that the company will be required to provide more evidence that the elevation in blood pressure does not also elevate potential for cardiovascular risk. This appears to be good news for VIVUS in that no additional clinical studies may be necessary.

If and when the product does enter the market there are residual doubts on the overall marketability of Qnexa, given that both agents of the combination are available as cheap generics. Despite this, Thomson Reuters Proprietary Forecasts predict peak sales of \$633.9 million by 2018, which reflects the magnitude of the opportunity in the obesity market.

QNEXA: FORECAST REVENUE (MILLION US\$)



* Data are derived from Thomson Reuters Forecast

IS THERE HOPE IN THE PIPELINE?

With the high profile products Lorcress and Qnexa held up at the starting block, the outlook for pipeline obesity products should be decidedly bleak. Some analysts are of the view that the FDA is requiring new obesity agents to exhibit safety and efficacy profiles similar to a regime of diet and exercise, a seemingly unrealistic expectation. Are there any pipeline products likely to satisfy such strict clinical specifications?

OREXIGEN'S COMBINATION HOPEFULS

Orexigen's Contrave, a sustained-release oral combination, will be next up for assessment at the FDA, with a PDUFA date slated for January 2011. Orexigen has adopted a similar strategy to VIVUS, developing an effective weight loss combination from existing products with many years of treatment experience to produce a synergistic effect.

The dopamine agonist, bupropion, is known to cause modest weight loss as monotherapy and is already used off-label for this purpose. Contrave combines bupropion with the opioid antagonist naltrexone. Orexigen is also developing for the severe obesity patient population Empatic, a combination of bupropion and zonisamide. All three of these drugs are available as generic forms but they are relatively expensive and it would be difficult to replicate doses used in Orexigen's formulations, which are protected by an extensive family of patents.

Trials indicate Empatic could induce substantial weight loss. Empatic side effect profile looks attractive too, with no serious adverse events in clinical trials to date. Headache, insomnia, nausea and urticaria were highlighted as key side effects. There were no reports of changes in cognitive function, depression, suicidality or anxiety in the 24-week trial. Weight loss did not plateau which suggests further weight loss will be seen in trials of longer duration. In a 48-week trial, Empatic treatment reduced body weight by 15% in healthy obese people in the absence of diet and exercise.

Contrave has also shown excellent weight loss in clinical trials in over 5000 patients and of the two products arguably has the greatest market potential as it addresses a larger patient population. Improvements in waist circumference, blood pressure, triglycerides, HDL, and blood glucose levels were also identified. Contrave also has an intriguing potential for treating craving associated with overeating and depression, a co-morbidity affecting a large proportion of obese patients, given that both agents are licensed individually to treat addiction and bupropion is an antidepressant.

Although Contrave is unlikely to satisfy FDA requirements for a placebo-like adverse-event profile, perhaps of all the recent contenders up for approval, it has the best safety profile. The most common treatment-related adverse events reported in clinical trials were tolerability factors of dizziness, constipation and nausea. Nausea subsides with use, Orexigen reports, suggesting there is potential for up-titrating the dose to control levels of nausea and that it will become less of an issue with treatment experience.

The clinical attributes of efficacy combined with acceptable tolerability suggest Contrave is one of the best placed products to gain approval for obesity in an increasingly difficult regulatory environment, and its revenue could exceed any obesity product seen to date. *Thomson Reuters Forecast* estimate peak sales by 2018 of \$918 million.

EMERGING TYPE 2 DIABETES AGENTS ARE EFFECTIVE WEIGHT LOSS AGENTS, BUT ARE THEY TOLERABLE?

In the search for an anti-obesity agent with placebo-like tolerability, many had been hopeful that the emerging type 2 antidiabetic agents, the injectable GLP-1 analogs Victoza (Novo Nordisk's liraglutide) and Byetta (Eli Lilly's exenatide), and Amylin's amylinomimetic pramlintide would fit the bill. All of these agents have demonstrated weight loss in clinical trials, and the fact that they are licensed for long-term use in type 2 diabetes, indicates their side effect profile would be acceptable to the regulatory authorities.

Weight loss has been lauded as one of the key selling points of Byetta, with clinicians favouring the use of this drug in type 2 diabetics for its ability to reduce weight rather than blood glucose levels. However, the post-marketing arena has not been plain sailing for Lilly's Byetta. Its label was recently amended with a black box warning of hemorrhagic and necrotizing pancreatitis, and renal impairment and failure. Preclinical studies have also indicated a potential link to thyroid cancer. These factors will likely curtail any off-label use in obesity, and create a barrier for an independent obesity indication on the label. Similarly, Victoza, another hopeful, contains a black-box warning of increased potential risk of thyroid cancer. Nausea and risks of pancreatitis are also prominent side effects of Victoza. Novo Nordisk has completed enrolment of patients without diabetes in a phase III obesity trial, however, this trial had been placed on hold until discussions with the FDA took place in June 2010. The trial will now commence in 1H11, but, given the recent attitude of the regulatory authorities towards anti-obesity agents, the black-box warning and lingering doubts over tumorigenicity may reduce its chances of approval.

Pramlintide side effects are mild-to-moderate, with nausea the most common adverse event reported. However, for treating diabetes, pramlintide needs to be injected three times daily. A similar treatment regime for obesity would restrict its use to highly motivated patients. Given that GLP-1 analogs and pramlintide are also injectables; obese patients would be committing themselves to inconvenient and potentially painful injections for the long-term and it is likely that compliance would be a major issue.

The oral antidiabetic SGLT-2 inhibitor canagliflozin is a long-term possibility for obesity. In clinical trials for diabetes canagliflozin demonstrated 2.3 to 3.4% decrease from baseline in body weight. Individuals with a natural genetic mutation that simulates SGLT-2 inhibition display only benign side effects, suggesting that SGLT-2 inhibitors will have a relatively clean side effect profile, though an obesity indication is still many years away for this drug class.

NOVEL TREATMENT CONCEPTS

There are several potential earlier stage pipeline candidates for anti-obesity: Norgine's synthetic non-systemic lipase inhibitor, cetilistat, which is under development by Takeda, Neurosearch's monoamine reuptake inhibitor tesofensine, Shionogi's velneperit, a once-daily oral neuropeptide Y5 antagonist, and 7TM Pharma's synthetic analog of PYY3-36 and pancreatic polypeptide obinipitide. Of these potential agents, cetilistat is furthest ahead in its development program, with phase III trials underway since December 2008. Cetilistat has the same mode of action as Xenical, and potential for GI side effects is therefore a concern. Clinical trials indicate its weight loss efficacy is modest though similar to Xenical, but the drug will need to display a much improved tolerability profile to displace Xenical. Phase II trials suggest GI side effects are more prevalent with Xenical, but further trial data will be required to substantiate this finding.

The three other candidates represent novel modes of action for the obesity platform. Obesity is a complex disease that is challenging to treat. What works for one patient may not work for another, thus there is a window of opportunity for agents with new treatment concepts. Phase II drug tesofensine, which modulates appetite and increases metabolic energy expenditure and fat metabolism, has demonstrated promising efficacy and good tolerability, with no abuse potential. Investigators state that in studies TIPO-1 and TIPO-4 tesofensine induced at least twice the level of weight loss of currently available drugs. The most notable adverse events in trials were dry mouth, GI disturbances and insomnia. Although a small cardiovascular safety study showed a placebo-like profile, potential for heart rate and blood pressure increases will be a cause for concern for the regulators, given that 5-HT and norepinephrine reuptake inhibitor Meridia was withdrawn in key markets due to its propensity to increase risk of cardiovascular disease. Neurosearch will need to have a carefully planned development program for this product to satisfy the approval bodies. The company aims to discuss this plan with EU and US regulators by the end of 2010. Phase III trials are currently on hold while the company seeks a suitable licensing partner.

SECTION II

DEALS HIGHLIGHTS

It is a well known fact that obesity is an urgent unmet medical need, affecting patients on a worldwide basis. However, it is interesting to see that in terms of partnering activity, companies continue to actively forge obesity-related deals, dating as far back as the early 1990s (on *Thomson Reuters Pharma*, over 200 Deals cover obesity as a therapeutic indication). The notion of ensuring the longevity of partnerships is widely recognized as an important factor when signing profitable deals.

Whilst partnering activities at present seem to continue at a steady rate, trends and observations have illustrated that conventional partnering models are changing. It has been suggested that partnerships are harder to maintain, which may be due to various reasons, such as economic and/or business strategy constraints. Ideally, companies strive towards forging deals that are of mutual benefit for all parties involved but also utilize budgeted capital in an economical way, which can be a challenge. Federal and venture capital funding remains a viable option as financial relief towards research and development expenses. However, it is not always a stable or guaranteed monetary avenue to follow when advancing an innovative and extensive product portfolio. Enhanced asset outlicensing and inlicensing activities, as well as mergers and acquisitions, are becoming increasingly seen as a 'quick-fix' option to help resolve revenue stream issues, which represents a significant change to traditional partnering models and dynamics. This change is a popular topic discussed at regular partnering conventions and conferences.

The major partnering players in the obesity arena include the common prolific pharmaceutical companies, such as GlaxoSmithKline (GSK), Roche, Abbott Laboratories, Takeda, Eli Lilly and Amylin.

XENICAL'S ESTABLISHED PARTNERING PORTFOLIO

Pharma conglomerate GlaxoSmithKline (GSK) acquired exclusive OTC commercialization rights in the US to Roche's gastrointestinal lipase inhibitor Xenical in July 2004. GSK further demonstrated its interest in the product by entering into a US co-promotion deal with Roche for prescription Xenical eight months later. This partnering activity across OTC and prescription use of Xenical exemplifies the commercial clout of the product as well as a cost-effective treatment option.

Following Chugai's decision to discontinue its development commitment to Roche's lipid uptake inhibitor in April 2005, the companies decided to seek out potential licensing players to further advance the product's development in Japan. By January 2009, GSK had gained full global commercialization rights to the product. GSK granted Taisho Pharmaceutical development and commercialization rights to the product in Japan. Utilizing GSK's skilled expertise and know-how with well-established product Alli, the two parties were to collaborate on providing the product to Japanese consumers. Specific financial terms were not disclosed.

LICENSING COMPANY	PARTNER COMPANY	DEAL START DATE	DEAL VALUE (US \$)*
Roche	GlaxoSmithKline	July 2004	Undisclosed
GlaxoSmithKline	Taisho Pharmaceutical	January 2009	Undisclosed

SUMMARY OF XENICAL'S AGREEMENTS

* Approximate values based on the achievement of all milestones for the principal components included in the deal.

"GSK's experience in OTC switches, their marketing capability and expertise in Consumer Communications were the factors that helped us identify GSK as our preferred partner."

Franz B Humer, CEO of Roche

PIONEERING ANTI-OBESITY THERAPEUTIC MERIDIA

Meridia, the first serotonin/norepinephrine reuptake inhibitor, was originally launched by New Jersey-based Knoll Pharmaceutical. As a result of Abbott Laboratories' acquisition of Knoll in December 2000, Abbott took over all ownership to the oral appetite suppressant. Despite the product's withdrawal from the market in October 2010, its partnering portfolio remains active (particularly in Asia).

In early January 1998, Eisai signed a collaborative development and marketing deal with Knoll for the product in Japan. The terms of the deal specified that since clinical development in Japan would be carried out by both companies, the development costs were expected to be shared equally. Japanese company Hokuriku Seiyaku assumed marketing responsibilities for the product in Japan for Knoll. In April 2004, the agreement was amended whereby Eisai acquired full Japanese development, marketing and promotion rights to Meridia. The partnering activity between such prolific players in this notoriously difficult, and occasionally unpredictable, region further strengthens the product's market potential in this territory.

A further deal centred on Meridia covered the AstraZeneca acquisition of European, Australian, Asian and South African marketing rights in September 1999. Specific financial terms of the deal were not disclosed at the time. However, it was reported that in certain territories, the companies were expected to jointly market the product, but AstraZeneca retained exclusive rights in four undisclosed Nordic countries. Unfortunately, the potential revenue of this deal was not realized, as the deal ended in February 2000.

LICENSING COMPANY	PARTNER COMPANY	DEAL START DATE	DEAL VALUE (US \$)*
Knoll Pharmaceutical	Eisai	January 1998	Undisclosed
Knoll Pharmaceutical	Astrazeneca	September 1999	Undisclosed

SUMMARY OF KNOLL'S OBESITY-RELATED AGREEMENTS FOR MERIDIA

* Approximate values based on the achievement of all milestones for the principal components included in the deal.

CONTRAVE'S BILLION-DOLLAR DEAL WITH NORTH AMERICAN LICENSEE TAKEDA

One of the highest-valued deals signed in the obesity arena was forged between private clinical stage company Orexigen Therapeutics and public Japanese pharmaceutical firm Takeda Pharmaceutical for Contrave, a sustained-release oral combination of the opioid antagonist naltrexone and the dopamine antagonist bupropion, in September 2010. As part of the deal, reportedly worth more than \$1.05 billion, Takeda obtained exclusive North American (US, Canada and Mexico) commercialization rights to the product, with Orexigen retaining co-promotion rights to Contrave in the U.S. Orexigen expected to receive an upfront cash payment of \$50 million from Takeda. Orexigen was also eligible to receive payments of over \$1 billion based upon the achievement of certain regulatory and sales-based milestones. Should Contrave reach commercialization, Takeda was committed to pay Orexigen double-digit tiered royalty payments on net sales in the territory. Orexigen and Takeda were to work together on ongoing development of the product, with Orexigen leading pre-approval activities, and Takeda leading post-approval activities. The parties expected to share any future development costs.

"This alliance allows us to successfully market one of our most important innovative products in one of the world's largest marketplaces."

Dr Thorlef Spickschen,
Chairman of the Knoll Board of Executive Directors

"Takeda is an ideal partner for Contrave given its proven track record in commercializing innovative medicines and its commitment to the treatment of obesity. We believe this is a great strategic partnership to enable our goal of a strong market entry for Contrave, if approved."

Michael Narachi, President and CEO of Orexigen

Other forged deals for Contrave included a manufacture deal between Orexigen and Patheon signed in March 2010; and an intellectual property deal for certain formulation patents related to bupropion between Orexigen Therapeutics and GSK in June 2009, whereby GSK was expected to receive upfront and milestone payments in exchange for these rights.

LICENSING COMPANY	PARTNER COMPANY	DEAL START DATE	DEAL VALUE (US \$)*
Orexigen Therapeutics	Takeda Pharmaceutical	September 2010	>1.05 billion (plus royalties)
Patheon	Orexigen Therapeutics	March 2010	Undisclosed
GlaxoSmithKline	Orexigen Therapeutics	June 2009	Undisclosed

SUMMARY OF CONTRAVE'S AGREEMENTS

* Approximate values based on the achievement of all milestones for the principal components included in the deal.

PROLIFIC DEAL-MAKING AMONGST EFFECTIVE WEIGHT LOSS AGENTS

Despite its launch as an antidiabetic agent, a major deal signed between Eli Lilly and Amylin Pharmaceuticals for Byetta demonstrates the products' potential in the obesity arena. The companies signed a global collaborative agreement on the development and commercialization of Byetta (including long-acting release formulations) in September 2002, potentially worth up to \$325 million. Eli Lilly was to make an initial non-refundable payment to Amylin worth \$80 million and purchase \$30 million of Amylin common stock. Eli Lilly was also expected to pay Amylin up to \$85 million for the achievement of certain development and product profile milestones. These milestones were convertible into Amylin equity at Eli Lilly's option. Eli Lilly was obligated to make additional future payments to Amylin of up to \$130 million contingent upon global commercialization of the product. US development and commercialization costs were expected to be shared equally, while development costs outside the US were to be shared between Eli Lilly and Amylin (80:20, respectively). Eli Lilly was responsible for all commercialization costs outside the US. The parties were to share US co-promotion, while Lilly was to be the exclusive marketer in all other countries. Operating profits from US sales were expected to be shared equally. Outside the US, operating profits were expected to be divided between Lilly and Amylin (80:20, respectively). In December 2003, Eli Lilly paid Amylin a \$35 million milestone payment for completing phase III trials. Also at that time, Eli Lilly relinquished rights to convert the milestone payment into Amylin common stock. Eli Lilly made a further milestone payment to Amylin in July 2004, following positive results from a type 2 diabetes trial. By July 2007, Amylin had received a \$15 million milestone from Eli Lilly for the launch of the drug in Europe.

Novo Nordisk acquired an exclusive option to California-based pharmaceutical company Scios' insulinotropin GLP-1 technology in May 1996. The option was exercised four months later. The exercised option covered patents, intellectual property and technology relating to a series of GLP-1 agonists, including emerging type 2 antidiabetic agent Victoza. Under the financial terms of the deal, Scios was expected to receive an undisclosed upfront payment, as well as milestone payments and royalties.

As part of a deal covering amylin analogs, Amylin and Johnson & Johnson (J&J) were collaborating on the development of pramlintide by June 1995. In August 1996, J&J's subsidiary LifeSpan decided to extend the collaboration for a further \$22 million. As part of this extension, Amylin received \$7 million in milestone and option payments, as well as a \$15 million equity payment upon review of two 1-year phase III trials.

The deal was further expanded to cover the development of second generation amylin analogs. J&J was to fund 50% of development costs and 100% of prelaunch costs for pramlintide. In June 1997, the collaboration was extended by a further \$3 million to include amylin agonists for the treatment of all diseases. However, in March 1998, it was announced that J&J expected to withdraw from the collaboration in September 1998, as a consequence of unsatisfactory initial phase III results. Despite termination of the deal (reportedly worth more than \$25 million), it is evident that revenues received as part of the deal helped advance the development of the product amongst well-established competitor products such as Xenical.

DRUG	LICENSING COMPANY	PARTNER COMPANY	DEAL START DATE	DEAL VALUE (US \$)*
Byetta	Amylin Pharmaceuticals	Eli Lilly & Co	September 2002	<325 million
Victoza	Scios	Novo Nordisk	May 1996	Undisclosed
Pramlintide	Amylin Pharmaceuticals	Johnson & Johnson	June 1995	>25 million

SUMMARY OF BYETTA, VICTOZA AND PRAMLINTIDE AGREEMENTS

* Approximate values based on the achievement of all milestones for the principal components included in the deal.

NOVEL CETILISTAT'S PARTNERING HIGHLIGHTS

Cetilistat is emerging as a potentially significant and novel therapeutic for obesity management. UK biopharmaceutical firm Alizyme granted Takeda exclusive Japanese development rights to cetilistat for the treatment of obesity and related diseases, including type 2 diabetes, in August 2003. Under the terms of the deal, Alizyme was expected to receive an initial \$2 million upfront payment, as well as additional milestone payments of up to \$40 million. Takeda was to pay for all development and commercialization costs in Japan and pay royalties on Japanese sales. In January 2004, Takeda exercised its rights to an exclusive license to develop and market cetilistat in Japan, after a detailed review of the European phase IIb clinical trial data. In return, Alizyme received a \$3 million payment. Alizyme received further milestone payments in January 2006 and in September 2008 for the initiation of phase II and phase III, respectively, with a combined worth of \$5 million. However, due to Alizyme halting all trading of its shares, the company went into administration in July 2009. This resulted in Norgine acquiring full global rights to the product from Alizyme in October 2009, including the partnership agreement with Takeda. Financial terms of the drug acquisition deal included a cash payment and a share of certain future revenues.

"This collaboration marks an important achievement for Alizyme as it is the first step in the commercialization of our product portfolio."

Dr Richard Palmer, CEO of Alizyme

CONCLUSION

At the present time, accessing what is potentially one of the largest and most lucrative pharmaceutical markets seems unattainable. There exists a high safety bar for approval of new products, and there is a history of high profile withdrawals in the category due to findings of unacceptable safety risks with taking these drugs. As yet, no drug has achieved the dream of the anti-obesity market, being capable of inducing >10% weight loss with a placebo-like side effect profile.

Still, there is a huge unmet medical need to treat patients who are clinically obese, not least because of the serious, debilitating and life-threatening co-morbidities associated with obesity. This means that there is a window of opportunity for drugs with acceptable tolerability and the best of these drugs in terms of efficacy and safety could still achieve blockbuster status.

Recent events at the FDA, where the regulators are ever more cautious, suggest novel agents will need to display robust efficacy and good tolerability to make the grade. Well executed strategies for pre-approval clinical trials will be required to ease products through the approval process. The raft of product withdrawals in recent years suggest that companies will also need to have well-designed post-approval strategies to reassure the regulators that they are poised to limit risks and assess adverse event rates in the post-approval arena.

AstraZeneca continues to emerge as a prolific deal-maker in the obesity arena. The pharmaceutical giant signed a deal in January 2007 with Palatin Technologies, which covered a series of small-molecule and peptidic melanocortin receptor-4 (MCR-4) agonists. The deal was reportedly worth more than \$320 million. AstraZeneca also acquired rights to Biovitrum's preclinical leptin modulator program, as part of a deal worth more than \$265 million. As more partnerships relating to early- and late-stage anti-obesity therapeutics emerge, it is clear that the current deals landscape will dramatically change. In addition, the increased prevalence of intellectual property agreements surrounding novel drug combinations may also impact the current partnering cycle of well-established agents and emerging obesity agents in the future (e.g. the intellectual property deal between GSK and Orexigen in June 2009).

The fact that obesity is one of the largest ever potential drug markets, and that it is virtually untapped, suggests that in the coming years there will be plenty of exciting development efforts and new treatment strategies arising from the ashes of the latest round of obesity rejects and withdrawals.



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