
Assessment of the U.S. Fibromyalgia Market in Support of S1 Filing (Phase 2)



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Executive Summary (Page 1 of 3)

- TONIX Pharmaceuticals is developing a new formulation of cyclobenzaprine for use in the treatment of fibromyalgia syndrome (FMS). The company has engaged Frost & Sullivan to assess this market opportunity, develop a market forecast through the year 2018, and investigate various aspects of the target market. In doing so, Frost & Sullivan has used extensive secondary research, as well as primary research interviews with 12 physicians engaged in the treatment of fibromyalgia patients.
- Fibromyalgia presents with a variety of symptoms that are common to other diseases, including widespread pain, tenderness, sleep disturbances, fatigue, headaches, depression, anxiety, and gastrointestinal disturbances. The underlying mechanism is not understood and there is no pathognomonic sign available for differential diagnosis. As a result, FMS has long been considered, at best, a diagnosis of exclusion and, at worst, a neurosis or simple malingering. In recent years; however, many healthcare providers have come to realize that fibromyalgia is truly a discrete medical condition. There are specific diagnostic criteria propounded by the American College of Rheumatology (ACR) and a number of treatment regimens that can provide significant relief to patients.
- The treatments applied to FMS are varied, and most often consist of a combination of medications with lifestyle changes. The majority of physicians use an empirical approach, varying the drugs and dosages they administer until they find what works best for each patient. Titrating drugs to find the optimal dose and using them in combinations that are found to provide optimal relief for each patient are the norm. FMS is seen as a lifelong disease that rarely resolves completely, and the goal of treatment is not eliminating the disease, but managing the symptoms to allow the patient to undertake the normal activities of daily life.

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- The market model, developed by Frost & Sullivan, indicates a significant potential for TONIX's TNX-102 product, with forecast sales of slightly over \$235 million in 2018. Primary research also revealed that, at present, cyclobenzaprine represents approximately 35% of the use of muscle relaxants in treating fibromyalgia.
- The physicians surveyed were divided into two groups, five specialists providing secondary and tertiary care, and seven primary care physicians (PCP). This revealed a significant difference in the use of muscle relaxants, including cyclobenzaprine, with PCPs using far more of these drugs than the specialists. In fact, the only three physicians interviewed who did not use any cyclobenzaprine were all tertiary care providers at academic medical centers. The PCPs were also much more aware of the economic issues facing their patients, with five out of seven naming the high cost and lack of insurance coverage as the principal barriers to using a new drug (compared to zero out of five specialists).
- The physicians interviewed generally expected the number of FMS patients to continue increasing, primarily due to a combination of increased awareness and acceptance of the disease and the development of improved diagnostic criteria. Major unmet needs that were identified, in decreasing order of the number of physicians stating them, were more effective medications, greater awareness and education, understanding of the underlying disease mechanism, and better insurance coverage for treatments.

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- The physicians interviewed were presented with target product profiles to review. These were received favorably. Most physicians (83%) agreed they would use TNX-102 with their patients: 50% would prescribe it for 5% to 15% of their FMS patients, while the remainder would prescribe it for 30% to 40%. Primary use would be as combined therapy together with other drugs. Only a minority of the physicians felt that they did not offer anything new. There was also some skepticism about the claim that they would lessen the need for using concomitant drugs.
- Currently, there is little in the clinical development pipeline for fibromyalgia, though some of the many pain drugs currently under development could conceivably compete in the fibromyalgia market. The FDA recently rejected Jazz Pharmaceuticals' NDA for sodium oxybate (Rekinla®). While the FDA showed no reservations towards its efficacy for the treatment of FMS, concerns related to drug abuse and control were raised. The company has indicated that it may conduct further studies and provide a new risk evaluation and mitigation strategy (REMS) for their product. At this point, it is uncertain whether Rekinla will obtain FDA approval in the forecast period considered for this study.
- The main competition for TNX-102; however, is expected to be the large number of off-label generic drugs now being used. They will have the considerable advantages of low price and physician familiarity, and TONIX will need to demonstrate superior clinical qualities for TNX-102 to drive both physician acceptance and coverage by health insurers.

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Background (Page 1 of 2)

- **FMS** is a chronic disorder traditionally characterized by widespread musculoskeletal pain. However, in recent years, it has been shown that other characteristic symptoms include moderate to severe fatigue, sleep disorders, problems with cognitive functioning, irritable bowel syndrome (IBS), headaches (including migraines), anxiety, and depression.
- **Fibromyalgia is generally believed to be more prevalent in women because the female population diagnosed with FMS is larger than male population.** The incidence of FMS increases with the age. Although FMS has been considered to predominantly affect menopausal and post-menopausal women, some experts believe that the development of new, more comprehensive diagnostic criteria may help to identify cases in younger individuals. In fact, the ACR states the diagnosis is most frequently made between the ages of 20 to 50. By the age of 80, approximately 8% of adults meet the ACR criteria for FMS.
- Although **the cause of fibromyalgia is unknown**, researchers have several theories about what may trigger the disorder. Some scientists believe that FMS may be triggered by an injury, trauma or other stress, including psychological stress. This trigger may in turn affect the central nervous system (CNS).
- **Fibromyalgia may be associated with changes in muscle metabolism**, such as decreased blood flow, causing fatigue and decreased strength. Others believe that the syndrome may be triggered by an infectious agent, such as a virus, in susceptible people, but no such agent has been identified.

Background (Page 2 of 2)

- **Fibromyalgia is difficult to diagnose because most of the symptoms are commonly found in other disorders.** The most widely diagnostic criterion being used today is from the ACR. A person is considered to have fibromyalgia if he or she has widespread pain in combination with tenderness in at least 11 of 18 specific tender point sites. This criterion focuses on pain and; therefore, does not consider the other important FMS symptoms. While newer, more comprehensive diagnostic criteria are being developed, a number of patients being treated for fibromyalgia do not meet the ACR criteria and others could potentially be misdiagnosed.
- **Fibromyalgia treatment focuses on relieving symptoms.** There are three prescription medications approved by the U.S. FDA specifically to treat FMS:
 - **Lyrica®** (pregabalin), approved in June 2007
 - **Cymbalta®** (duloxetine HCl), approved in June 2008
 - **Savella®** (milnacipran HCl), approved in January 2009
- **Fibromyalgia patients are also treated off-label** with narcotic and non-narcotic analgesics, low doses of antidepressants, anticonvulsants, and muscle relaxants.
- **The treatment of fibromyalgia requires a comprehensive approach.** The physician, physical therapist, and patient may all play an active role in the management of fibromyalgia. Studies have shown that aerobic exercise, such as swimming and walking, improves muscle fitness and reduces muscle pain and tenderness. Heat and massage may also give short-term relief, as do stretching exercises, such as yoga and Tai Chi. Antidepressant medications may help elevate mood, improve quality of sleep, and relax muscles. Patients with fibromyalgia may benefit from a combination of exercise, medication, physical therapy, and relaxation.

Phase 2 Objectives

TONIX Pharmaceuticals has developed a bedtime cyclobenzaprine formulation for the treatment of fibromyalgia and successfully completed phase II clinical trials. The company wants to raise public funding through an IPO to further develop this key product.

Frost & Sullivan will leverage our significant consulting and market research capabilities, along with our extensive experience in the fibromyalgia market, to provide accurate, unbiased, and insightful deliverables. Our quality work, sound reputation, and the strong brand equity of the Frost & Sullivan name will ensure that our deliverables are well received by TONIX's management, board of directors, and other key stakeholders.

Phase 2 of this project addressed the following questions:

- Forecasting growth for fibromyalgia brands, including new product entries through the year 2018.
- Scenario analysis (base case and optimal case) for TONIX fibromyalgia products entering the market in 2015, including a three year forecast to 2018 after entering the market.

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Phase 2 Consulting Approach



- The future growth of the U.S. fibromyalgia market and individual product contributors was assessed by Frost & Sullivan through an analysis of the historical data collected in Phase I in combination with data gathered from in-depth interviews with 12 key opinion leaders (KOL), physicians with extensive experience in treating patients with fibromyalgia.
- Scenario analysis with the product profiles was assessed by Frost & Sullivan through an analysis of in-depth interviews with 12 KOL physicians and an analysis of physician uptake data for historical comparable drugs.

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A discussion guide and product profile were developed in collaboration between TONIX and Frost & Sullivan. Both were used to query respondents. The product profile was revised during the course of the primary research. These product profiles are included in the Appendix.

Frost & Sullivan's team then conducted 12 in-depth interviews with KOL physicians from ten states. Each of these physicians had ten years or more of experience in treating at least 100 fibromyalgia patients per year.

DEMOGRAPHIC CHARACTERISTICS OF THE PRIMARY RESEARCH SAMPLE

	Years of Experience	FMS Patients per month	%Treated with Cyclobenzaprine
Average	16.8	49.1	13.6%
Maximum	30.0	150.0	100.0%
Minimum	10.0	8.0	0.0%

Demographics (Page 2 of 2)

The first set of five interviews was held with KOL physicians involved in secondary or tertiary care of fibromyalgia patients. After consultation with TONIX, Frost & Sullivan conducted the remaining seven interviews with primary care physicians treating fibromyalgia patients.

PHYSICIAN SPECIALTIES IN THE PRIMARY RESEARCH SAMPLE

Specialty	Location	Type	Number
Neurology/Pain	University Hospital	Tertiary	2
Rheumatology	University Hospital	Tertiary	1
Psychiatry	University Hospital	Tertiary	1
Rheumatology	Community Hospital	Secondary	1
Family Practice	Office	Primary	7
TOTAL			12

A few differences were noted between the two groups of physicians. On average the secondary and tertiary care physicians treated 33.3% more fibromyalgia patients per month than the primary care physicians (51.6 versus 41.7 patients per month). Most significantly, the primary care physicians prescribed muscle relaxants, including cyclobenzaprine, far more often than the secondary and tertiary care physicians. All three of the physicians who never used cyclobenzaprine were providing tertiary care at university hospitals.

USE OF MUSCLE RELAXANTS IN THE PRIMARY RESEARCH SAMPLE

Type of Care	% of Patients Prescribed with Muscle Relaxants	% of Patients Prescribed Cyclobenzaprine
Primary	35.0%	20.0%
Secondary & Tertiary	14.7%	4.7%

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Market Overview – Summary of Phase I Results

Overall market figures

- Frost & Sullivan estimates that there were approximately six million patients with fibromyalgia in the United States in 2010.
- The total value of the market for fibromyalgia drugs was \$1.2 billion, growing at a compound annual growth rate (CAGR) of 18.4% per year from 2007 to 2010.
- The unit volume was 1,122.3 million minimum dosage units, growing at a CAGR of 1.2% per year from 2007 to 2010. The reason for the high growth in market value compared to unit volume was the recent introduction of three high-priced branded drugs with FDA-approved labeling for the treatment of fibromyalgia in the years 2007-2009.

Lyrica, Cymbalta, and Savella

- The three approved drugs accounted for \$887.5 million in U.S. fibromyalgia sales in 2010, representing 70.2% of the market, while all muscle relaxants garnered \$28.5 million in sales, or 2.3% of the market. Sales of muscle relaxants declined at a CAGR of 15.8% from 2007 to 2010, while a meaningful CAGR could not be assigned to the three approved drugs because a new one was approved in each of the years 2007, 2008, and 2009.

Pricing

- The average price per minimum dosage unit of muscle relaxants was found to be \$0.21 in 2010, declining at a CAGR of 1.1%. The average price per minimum dosage unit of all drugs for fibromyalgia was \$1.13, increasing at a CAGR of 17.1%. The highest priced drug was Cymbalta at \$3.68, while the fastest annual price growth from 2007 to 2010 was noted for Lyrica at 2.7%.

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Development of the Fibromyalgia Market Model (Page 1 of 3)

- A different procedure was used for forecasting TNX-102, Cymbalta, Savella, generic cyclobenzaprine and other muscle relaxants than was used for all other drugs and classes of drugs. This was due to the need to account for:
 - The likely impact of Cymbalta going generic in 2013, including the effect on sales of Savella.
 - The likely impact of TNX-102's market entry in 2015 sales of generic cyclobenzaprine and other off-label muscle relaxers
 - Physician acceptance of TNX-102 and its rate of uptake in the market
- For drugs and classes of drugs other than those listed above, the secondary research conducted in Phase I was expanded to develop projections of their dollar sales volumes for use in treating fibromyalgia in the United States through 2018. Their prices were then projected from the growth rates determined in phase 1, and their unit volumes were calculated as dollar sales divided by price.
- Primary research provided the data needed to separate the use of generic cyclobenzaprine from other muscle relaxants. When the physicians were asked what percentage of their use of muscle relaxants was represented by cyclobenzaprine, the average of their responses was 29.9%. However, when these responses were weighted for the size of their fibromyalgia patient populations, the resultant weighted average was 40.0%. These two numbers were then averaged to give an estimate that cyclobenzaprine represents 35.0% of all muscle relaxant use for fibromyalgia in the United States.

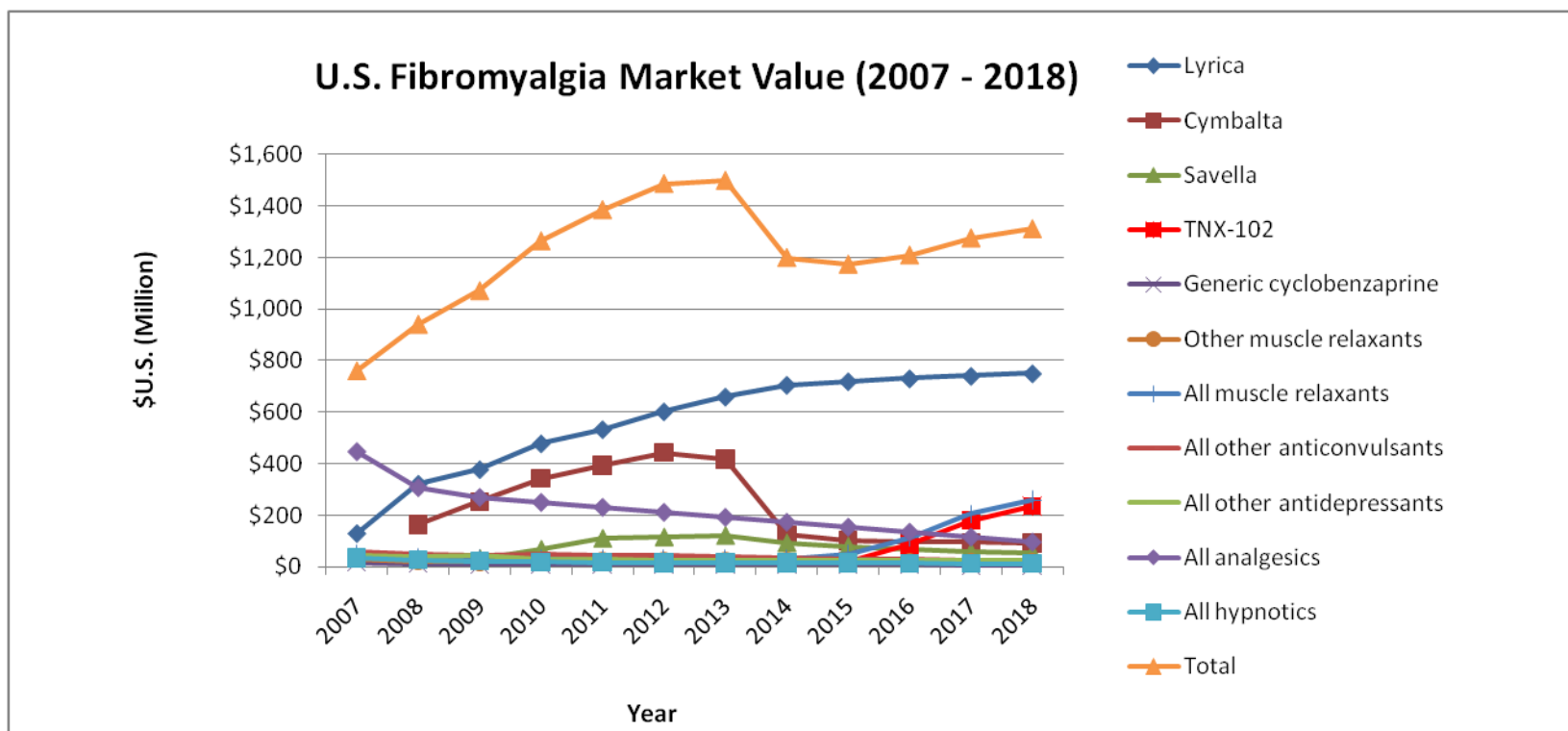
Development of the Fibromyalgia Market Model (Page 2 of 3)

- The initial pricing for TNX-102 was forecast to be \$5.93 per daily dose if it were available in 2010. This number was derived from taking an average of the retail prices of Lyrica and Cymbalta found on Drugstore.com, which was \$8.14 per day. This price was then discounted back to the manufacturer's ex-factory price. This was accomplished by comparing the retail prices of Lyrica and Cymbalta to the manufacturer's prices in the Wolters Kluwer database. This established a discount factor of 72.9%, which was then applied to the forecast retail price of TNX-102. The estimated \$5.93 price of TNX-102 in 2010 was then projected to grow at the same rate as Lyrica from 2013 through 2018. Lyrica's price growth rate was used since it was intermediate between those for Cymbalta and Savella.
- The unit volume of TNX-102 sales from 2015 to 2018 was projected as a percentage of the estimated total unit sales of drugs for FMS in that period. These percentages were derived from insights gained from primary and secondary research as well as from analysis of the market introductions of comparable drugs (Amrix[®], Fentora[®], Flector[®] and Ranexa[®]). The dollar volume of sales was then calculated as unit volume times price.
- The unit volumes of generic cyclobenzaprine and other off-label muscle relaxants were then adjusted to account for estimated losses due to the introduction and uptake of TNX-102. These estimated losses were based on insights gained from primary market research. Their prices were then projected from the growth rates determined in phase 1, and their dollar sales volumes were calculated as unit volume times price.

Development of the Fibromyalgia Market Model (Page 3 of 3)

- The unit volume of Cymbalta was adjusted to account for the effect of going generic, based on insights gained from primary research. The dollar volume of Cymbalta sales was determined from secondary research and the average price was calculated as unit volume times price.
- The unit volume of Savella was then adjusted to account for the effect of increased Cymbalta unit sales since Cymbalta is a direct competitor with the same mechanism of action. Savella's price was then projected from the growth rates determined in phase 1 and the dollar volume of sales was calculated as unit volume times price.

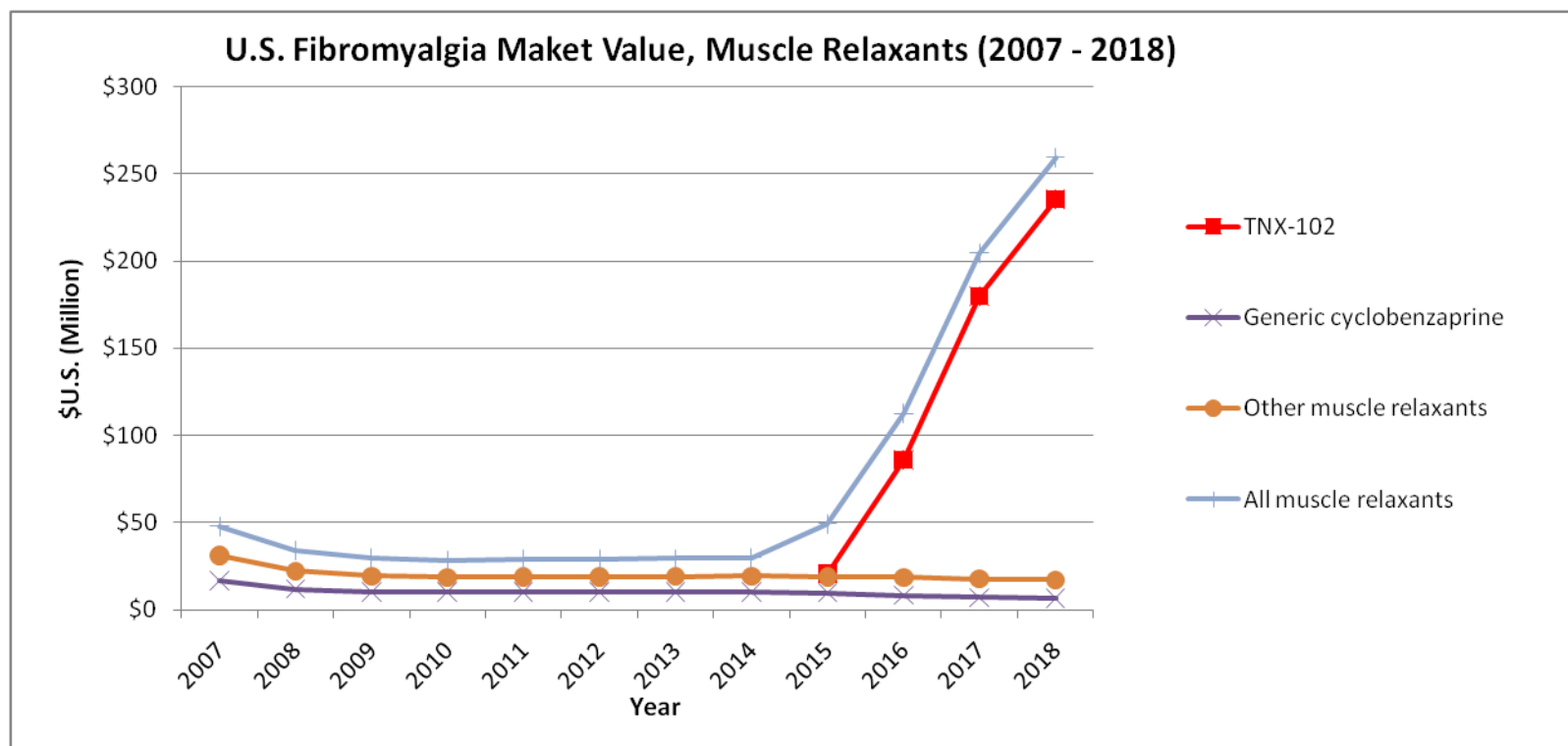
Fibromyalgia Market Value Forecast to 2018



Source: Frost & Sullivan analysis.

Total U.S. sales of drugs for treating fibromyalgia are forecast to increase to nearly \$1.5 billion in 2013, when Cymbalta will go generic. As a result, sales are forecast to drop almost 20% to just below \$1.2 billion in 2014, then increase at a CAGR of 2.2% through 2018. Lyrica is expected to maintain the highest sales throughout this period.

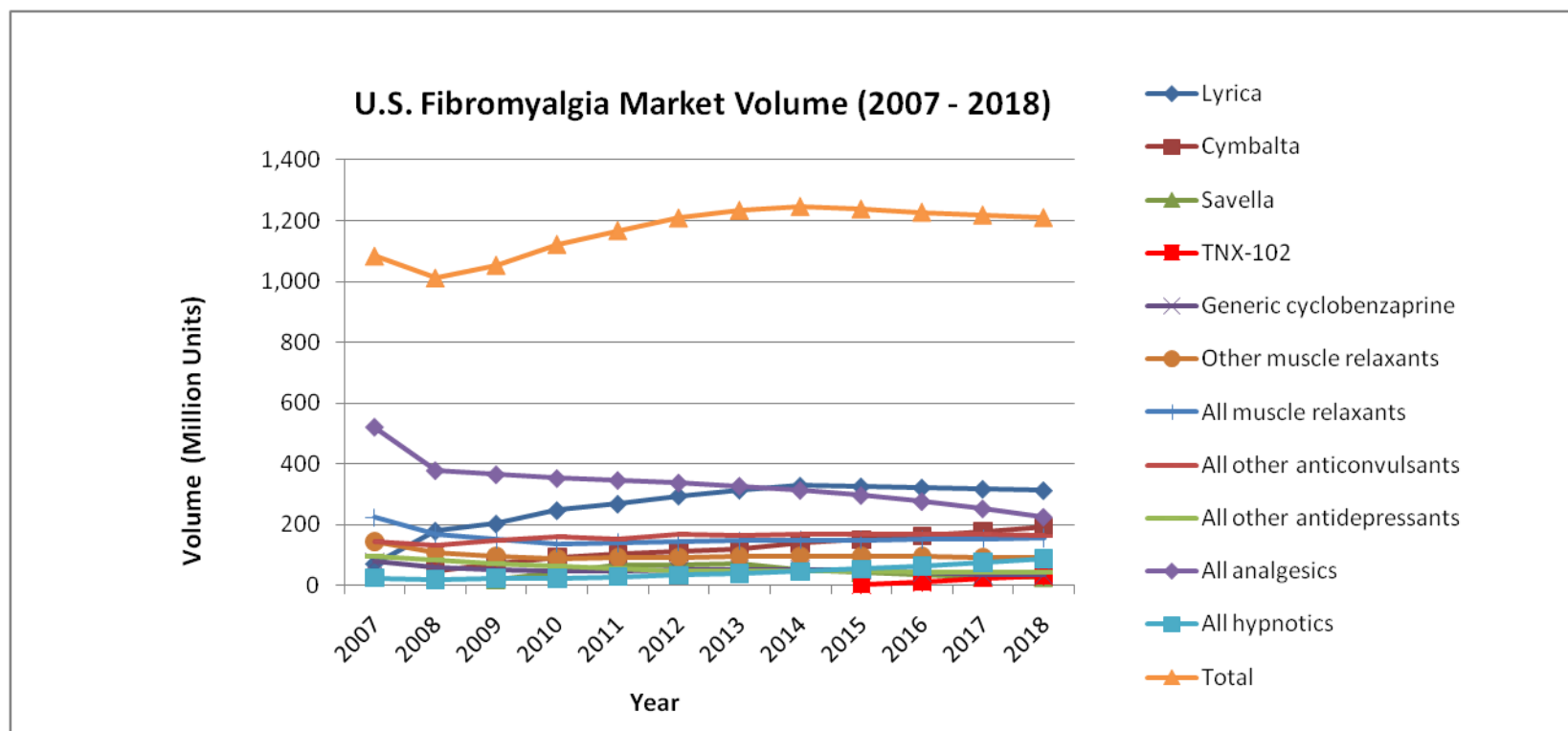
Fibromyalgia Muscle Relaxant Market Value Forecast to 2018



Source: Frost & Sullivan analysis.

Sales of generic cyclobenzaprine and other off-label muscle relaxants are projected to decline from 2011 to 2018. Although the introduction of TNX-102 in 2015 will result in a drop in the sales of off-label muscle relaxants, its uptake will lead to a surge in total muscle relaxant sales for FMS. TNX-102 sales are projected to surpass \$235 million in the United States in 2018.

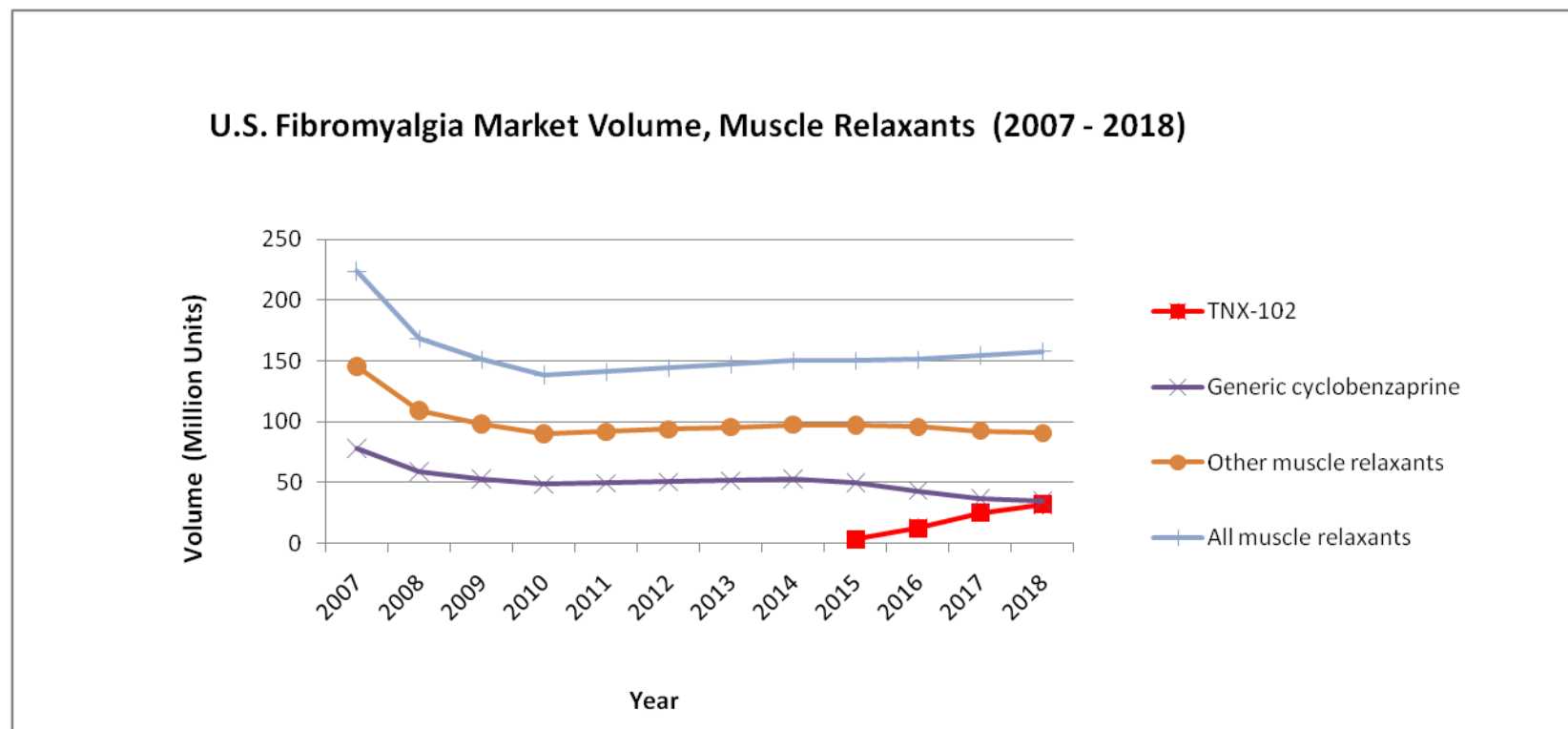
Fibromyalgia Market Volume Forecast to 2018



Source: Frost & Sullivan analysis.

The unit volume of drugs prescribed for the treatment of fibromyalgia in the United States is forecast to peak in 2014, then decline slowly at a CAGR of -0.7% through 2018. Although the volume of TNX-102 and Cymbalta sales is expected to increase during that period, this will be slightly more than offset by corresponding declines in the unit volume of Savella and off-label muscle relaxants, as well as continued declines in the volume of other off-label drugs for FMS, particularly analgesics.

Fibromyalgia Muscle Relaxant Market Volume Forecast to 2018



Source: Frost & Sullivan analysis.

The unit volume of muscle relaxants prescribed for fibromyalgia is forecast to increase at a CAGR of 1.7% from 2010 through 2018. It is expected to level off in 2014 due to declining sales of off-label muscle relaxants, the pick up again in 2016 due to the uptake of TNX-102. After the introduction of TNX-102. TNX-102 is projected to achieve sales of 32.0 million minimal dosing units in 2018.

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Fibromyalgia Treatment Overview (Page 1 of 4)

- **Fibromyalgia is mostly considered to be one condition that shows multiple symptoms.** Fibromyalgia is a syndrome characterized by a number of different symptoms (pain, fatigue, depression, tenderness, sleep disorders, etc). Each patient develops his or her own particular set of symptoms, which can vary from time to time. The physician's challenge is to find the pharmacological and non-pharmacological treatments that best address each case.
- **The diagnosis of fibromyalgia has evolved in recent years.** The ACR criteria which looks at 11 of 18 tender points is still the main assessment performed. Some physicians rely on this evaluation. However, most physicians consider the ACR criteria as one of the various assessments that should be performed while diagnosing an FMS patient, together with physical exams, patient history, exclusion of other conditions, and the evaluation of symptoms, including fatigue, sleep disorders, IBS, migraines, and other frequent signs of FMS.
- Some key opinion leaders agree that **15% to 20% of their patients do not meet the ACR criteria.** Most of the patients that do not meet these criteria are men.

Fibromyalgia Treatment Overview (Page 2 of 4)

- **Fibromyalgia is a chronic condition that does not resolve.** If untreated, it could last a lifetime. As patients get older, the syndrome does tend to stabilize. This is probably due to coping strategies developed by the patient.
- **The objective of FMS treatment is to drive pain levels down to what is manageable for each patient,** as well as reducing the presence of other symptoms, such as depression or insomnia. The ultimate goal is to allow the patient to increase their energy level and resume the activities of a normal life.
 - One PCP stated, “Medication can resolve acute exacerbation. But the disease itself does not go away, it gets better. The patient may feel better some days and sometimes not. There is not a cure for it, we just want to keep it under control.”
- **The chronic pharmacological treatment of fibromyalgia patients varies greatly from patient to patient and physician to physician.** There are no definitive treatment guidelines published, and most of these physicians use anything that they have found to work. This includes many combinations of on and off-label drugs and lifestyle changes (particularly exercise, stretching, and sleep habits). At the extremes, one physician stayed strictly with the three approved on-label drugs, while another often used non-pharmaceutical supplements.

Fibromyalgia Treatment Overview (Page 3 of 4)

- **The treatment of flares also varies from one physician to other.** Flares are a frequent feature with many patients. Patients are already on chronic pharmacological treatment, thus when a flare occurs physicians may:
 - Try not to change the current medication, but add mild exercise and rest
 - Increase the dosing of current medication (if possible)
 - Add a different medication, such as muscle relaxants (if not taking any) or even a narcotic, for the duration of the flare
- **Many physicians provide patients with a “flare package” of drugs to be used PRN.**
- **Most of the physicians in the survey waited four to eight weeks to see if a treatment was working and had no or at least tolerable side effects.** One determined the waiting period by the class of drug, waiting three to four days for sleep aids, two to three weeks for pain medications, four weeks for anti-depressants, and six to twelve weeks for Savella.

Fibromyalgia Treatment Overview (Page 4 of 4)

- **The treatment of fibromyalgia usually requires the use of a combination of drugs to address various symptoms.** However, two physicians preferred monotherapies.
- **Many pharmacological combinations are used.** One of the most frequent was Cymbalta (or another antidepressant) + Lyrica. One physician always paired a sleep medication with something for pain.
- **Muscle relaxants are primarily used as add-on therapies.** At lower doses (five to ten mg) for chronic treatments or to help improve sleep, or at higher doses (ten to twenty mg) for the treatment of flares.

Gender Incidence in Fibromyalgia

- **Female patient population currently diagnosed with FMS is larger male population.**
 - However, physicians thought that fibromyalgia syndrome equally affects women and men. The reason for the greater number of female patients may be a result of various behavioral aspects characterizing each group:

Female Patients

- More likely to express pain
- More willing to see doctors
- Generally have a lower pain threshold
- More likely to follow the doctor's orders

Male Patients

- Do not usually complain of pain
- Tend to go to the physician's office only when they can no longer stand the pain
- Generally have a higher pain threshold
- Often take OTC (over the counter) medications

- Some symptoms are more frequent among females (IBS, depression) and others among males (fatigue).
- One rheumatologist noted, "It is not recognized in men because they don't complain as much and drink more alcohol. I have to be quite frank; I have patients that drink eight to ten cans of beer per day or six double martinis and knock themselves out. They take OTC garbage, like ibuprofen, and end up with all kinds of things, like renal impairments. They borrow drugs from their friends; they don't keep their medical appointments. Women, on the other hand, see physicians more often. If you ask the right questions you'll see it equally for both."

Age Incidence in Fibromyalgia

- **Menopause is seen as one of the stress factors that could trigger the syndrome.**
- However, most of the physicians interviewed believe there is no direct relationship between age or reproductive cycle and the onset of fibromyalgia.
- Several of the physicians interviewed believed that lower rates of FMS in children and adolescents might be due to their younger bodies being more able to withstand the symptoms.
- As the diagnosis of fibromyalgia improves, the number of teens, pre-teenagers, and even children will increase. However, pediatricians are not yet prepared to diagnose FMS.
- One psychiatrist noted, “There is no connection with age, it can occur at any age. Incidence studies looks like there is, but only because of the duration of the studies. We’ve seen it even in teenagers and pre-adolescents.”

Pharmacological Treatment of Fibromyalgia (Page 1 of 3)

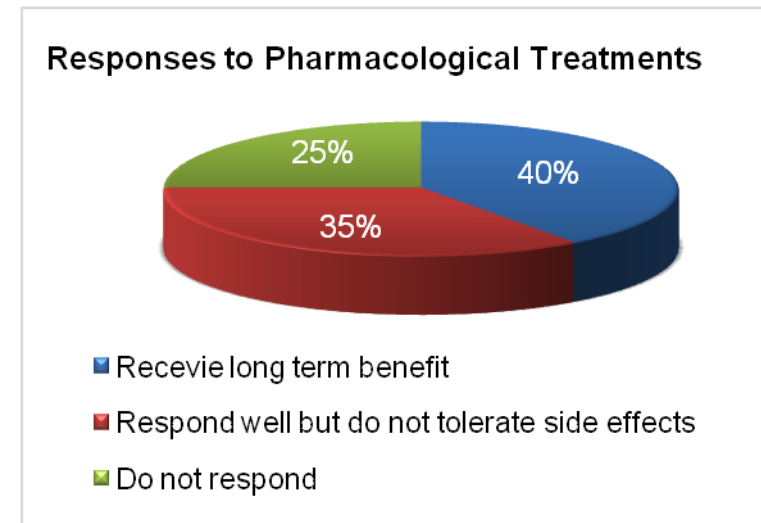
- **More than 50% of the physicians interviewed indicated that they first prescribe the FDA-approved drugs Lyrica, Cymbalta, and Savella.**
- Those that started treatments with generic drugs pointed out that health insurance coverage was the main reason.

Main Criteria Used to Decide on Pharmacological Treatment

- Insurance coverage and patient's financial situation
 - Pain levels
 - Other symptoms (fatigue, sleep disturbances, migraines)
 - Psychiatric co-morbidities (anxiety, depression)
 - Medical co-morbidities (sleep apnea, overweight)
 - Patient history of FMS pharmacological treatment
- **Cymbalta was by far the most preferred alternative**, specially for those patients suffering depression.
 - **Lyrica was the second-most preferred**, mostly for patients with no depression. Some physicians would not prescribe Lyrica or were concerned about its usage given side effects, such as peripheral edema.
 - **Savella was the least used** of the drugs approved for fibromyalgia due to its side effects, especially nausea.

Pharmacological Treatment of Fibromyalgia (Page 2 of 3)

- **Approximately 40% of patients receive a long term benefit (six to twelve months) with first line therapies**, once they have reached their optimal dosing after a titration period. This figure seems to be similar for the treatments most commonly used. The response is better in patients who are more motivated to take care of themselves by exercising and making lifestyle changes. These patients show good energy levels and can carry on their normal activities.
- **Thirty to forty percent of patients may have a good response to a drug, but cannot tolerate the side effects.** In this case, preferred alternatives are to reduce dosing and, if necessary, change the medication.
- **Twenty-five percent of FMS patients do not respond to treatments.** Similar rates are seen for each treatment.
- **In tertiary care, success rates can drop to 10%-20%** because patients have already seen various physicians and tried many different treatments.



Source: Frost & Sullivan analysis.

Pharmacological Treatment of Fibromyalgia (Page 3 of 3)

Percentage of Patients Presenting Each symptom

	At the Beginning of Treatment	After Treatment
Pain	100%	100%
Tenderness	100%	100%
Sleep disorders	96%	38%
Fatigue	92%	33%
Depression	71%	23%
Joint stiffness	68%	21%
Headaches (including migraines)	66%	22%
Anxiety	66%	20%
Gastrointestinal disturbances	65%	25%
Problems with cognitive functioning	61%	38%
Muscle spasms	58%	32%

Source: Frost & Sullivan analysis.

- Pain, tenderness, fatigue, and sleep disorders are the most frequent symptoms in fibromyalgia patients. Over 90% of patients present with these symptoms before starting a pharmacological treatment for FMS.
- With treatment, pain and tenderness will mostly improve to levels where patient can perform daily activities; however, they rarely disappear.
- Improvements in other symptoms are much more significant.

Unmet Needs in the Treatment of Fibromyalgia

Better, more effective treatments (8/12)

The primary identified unmet need was for better, more effective treatments for fibromyalgia symptoms (pain, fatigue, muscle spasms, sleep disorders). Current treatments are only partially effective. Few, if any patients, are ever seen to reach a completely pain-free state.

Greater awareness/education (5/12)

Most of the physicians surveyed believed that greater awareness and education of both physicians and patients would result in increasing numbers of patients being correctly diagnosed and coming in for treatment.

Understanding the underlying mechanism (4/12)

Several of the physicians surveyed pointed out that conducting research to understand the underlying etiology of fibromyalgia was key to developing more effective treatments, rather than just ameliorating the symptoms, which is all that is currently possible.

Improved insurance coverage (3/12)

Coverage of fibromyalgia pharmacological treatments is currently one of the most important restraints for prescription of FDA-approved drugs for patients with health insurance. Health insurers dictate treatment regimens, forcing physicians to prescribe cheaper generics even though they might not be the preferred option. In particular, several insurers require physicians to document treatment failure with Neurontin before they will provide coverage for Lyrica, while others will not cover it at all.

Fibromyalgia Treatment Trends

Fibromyalgia patient population will increase during the forecasted period.

- Most of the physicians surveyed (11/12) felt that the number of FMS patients would increase over the next few years, though not by any great amount. The primary reason given was greater awareness (7 physicians), followed by new and improved diagnostic criteria (6) and new drug approvals (5).
- The approval of the first drug for the treatment of fibromyalgia was in 2007 and recognition, management, and treatment of the syndrome has been improving every year.
- **Current treatment patterns will most likely not change significantly** unless physicians are able to understand the cause of the syndrome, resulting in more targeted treatments. However, **the expanded ACR criteria will lead to increased recognition** by doctors who are not currently treating fibromyalgia patients.
- **As new drugs are approved by the FDA**, manufacturers will promote them and; therefore, **raise awareness**. This will drive the attention of insurers to FMS, probably giving better coverage of its pharmacological treatments.

“Eighteen years ago when I was doing my residency, FMS was a diagnosis of exclusion and the patient was more on the nutty side. However, the more research is being done on this, FMS is more of a problem related to pain reception. And we all perceive pain differently than others, it does make a lot of sense. So, you need to find the treatment regimen for each person according to what their perception of pain is. With better education and training of physicians, plus increased awareness of patients, the number will keep increasing.”--- Primary Care Physician, MO

Reaction to Product Profiles

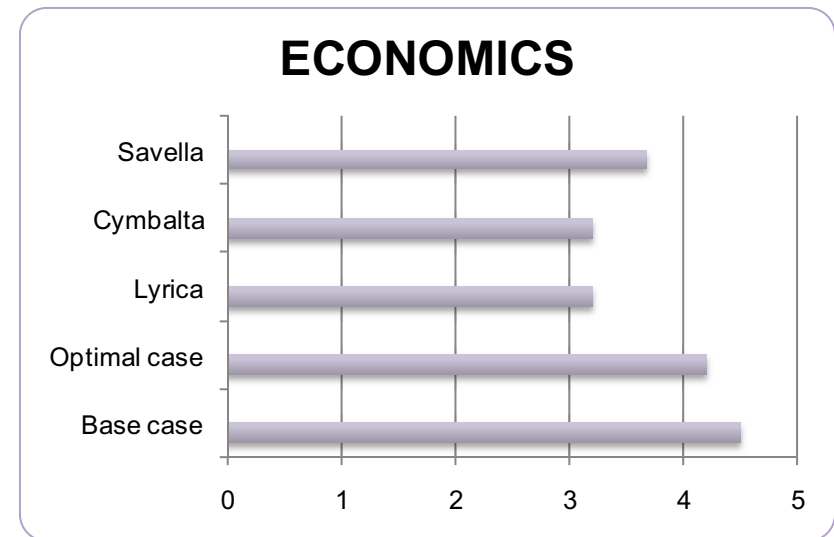
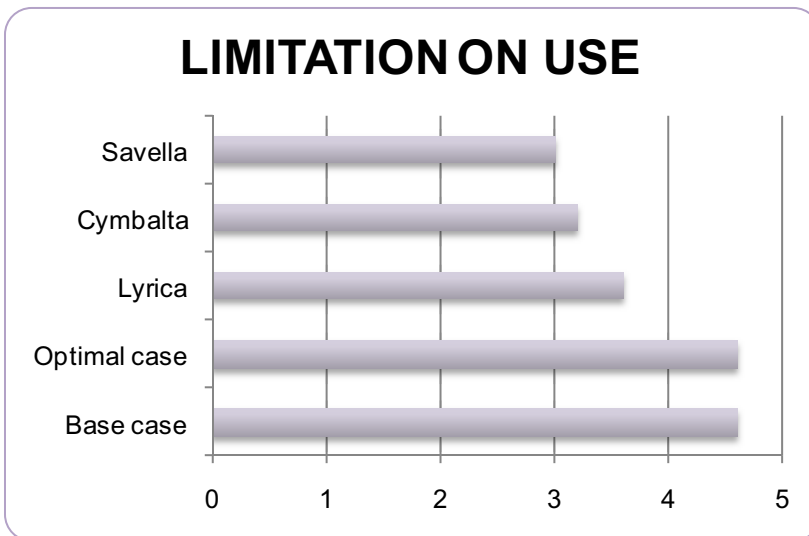
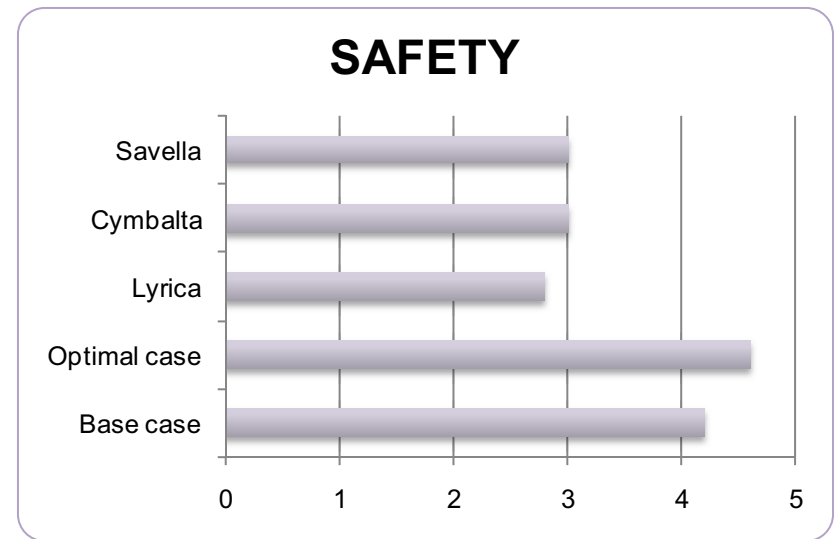
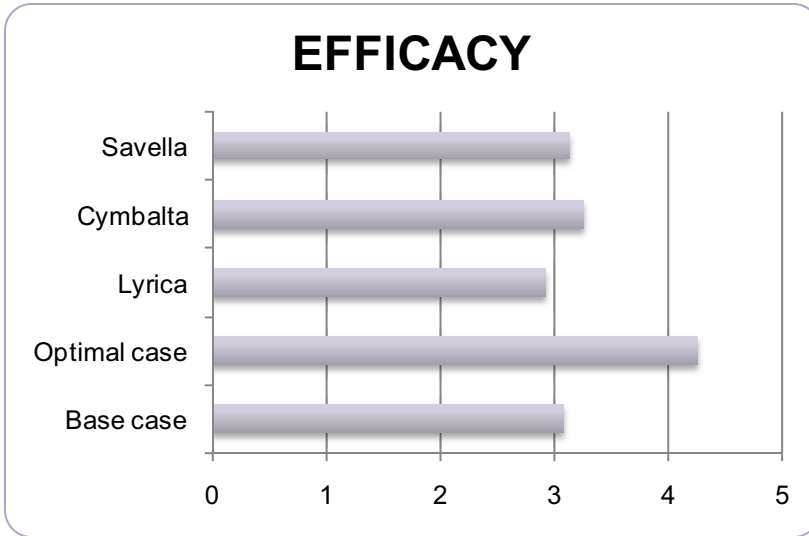
Product profiles methodology

- Two product profiles, including base and optimal cases for TNX-102, were presented to key opinion leaders in the treatment of fibromyalgia.
- These physicians were queried about their level of satisfaction related to both profiles, as well as to current drugs with FDA approval for the treatment of FMS. They graded four different factors on a scale from 1 to 5, with **1** being “**not satisfied at all**” and **5** being “**extremely satisfied**”.

The factors examined were:

- Efficacy
 - Safety
 - Limitation on use
 - Economics
-
- Based on the information gathered, Frost & Sullivan compared these drugs to assess how well positioned both target profiles were against currently approved drugs.

Average Ratings on a 5 Point Scale



Scale: 1 (not satisfied at all) to 5 (extremely satisfied)

Source: Frost & Sullivan analysis.

Advantages and Disadvantages

The two attributes receiving the most comments were the extent of pain reduction and the elimination of concurrent drugs. While some physicians agreed that the proposed percentage reductions were very good, others said that they were not enough or no different from what was already available.

POSITIVE OPINIONS

- “30% improvement is good.”
- “40% pain reduction is great!”
- “Improvement of functionality is excellent.”
- “The advantage is that it works on different things, that is huge.”
- “I like bedtime, that’s nice. Because people like taking something at bedtime and going to sleep.”
- “I like pain reduction with few precautions and DDI. Good if eliminates concurrent drugs.”
- “Product B seems very superior. I cannot see much disadvantage, I could use a little more information here ... it says there are less interactions, I cannot see a disadvantage.”

NEGATIVE OPINIONS

- “The idea of developing a formula that already has a generic, it’s very challenging.”
- “Nothing really great about either one. Nothing about it that I don’t have already.”
- “I didn’t like the concurrent drug doses, that makes them confusing which means interactions and more unreliable stuff.”
- “A 30% reduction in fatigue is nothing, because placebos do the same.”
- “Reducing a patient’s pain from 6 (on a scale of 10) to 4 is more like an 80% reduction.”
- “Eliminating the need for concurrent drugs is hard to believe.”

Potential Barriers

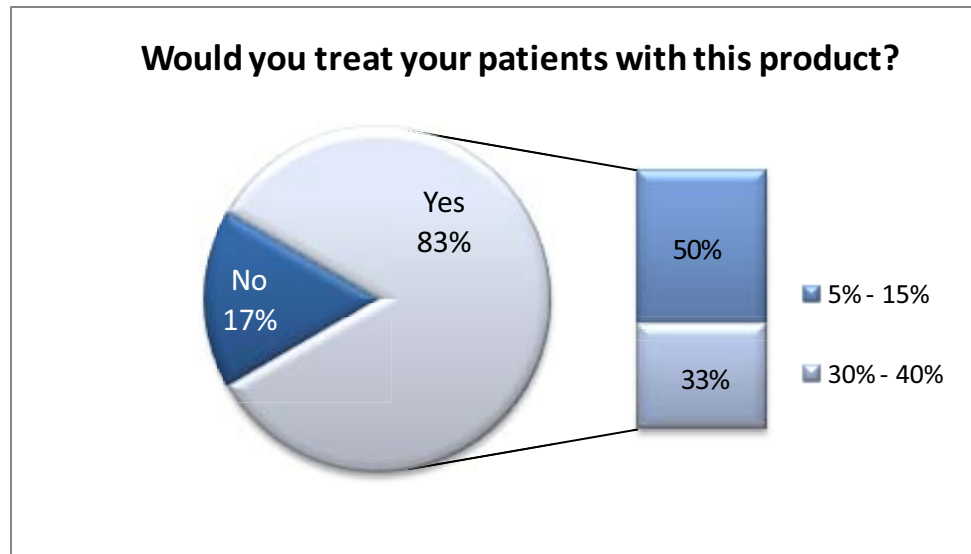
- According to these physicians, this new product will compete with all drugs already available in the market, with a higher intensity of rivalry with the cheaper, generic drug segment.
- Most important barriers that this new drug may encounter, according to interviewed physicians were: cost, insurance coverage, and physician reluctance.
 - Significantly, cost and insurance coverage were mentioned by five out of seven primary care physicians interviewed, but none of the secondary or tertiary care physicians.

• **Insurance Coverage and Cost:** Insurance coverage drives prescription patterns. In a market with so many generic drugs available, it is difficult to get coverage for an expensive new drug. Also, patients with no insurance coverage make their decision mostly based on the price of the drugs, hence physicians must consider this factor as well.

• **Physician Reluctance:** There are many physicians who would not want to give up on their traditional drugs, unless the new one works perfectly or is fully compatible with currently used ones.

Potential Market

- Most physicians (83%) would use this new product with their patients. However, 50% would only prescribe it for 5% to 15% of their patients, while the remainder would prescribe it for 30% to 40% of their patients.
- Within the group that would not use it, the main reason given was the adverse effects caused by cyclobenzaprine.



Source: Frost & Sullivan analysis.

- Most of the use of base and optimal profile drugs would be as a combined therapy with other drugs, as is normal practice.

Use of Muscle Relaxants

- During 2010, the use of **muscle relaxants** within the total U.S. fibromyalgia market accounted for **2.3% (\$28.5 million)** of its value and **12.3% (138.1 million units)** of its volume.
- There was a great deal of variation in the use of muscle relaxants in general and cyclobenzaprine in particular by the physicians in the survey. This ranged all the way from one who never used muscle relaxants or any other off-label product to another who administered cyclobenzaprine to virtually every FMS patient he saw.
- **Cyclobenzaprine is the muscle relaxant most widely used in the treatment of fibromyalgia. It represents 35% of both value and volume within the muscle relaxants segment.** Robaxin and Soma fall in second and third place, respectively. Others also used are Zanaflex, Baclofen, Skelaxin, and Parafon Forte.

Use of Muscle Relaxants in Treatment of Fibromyalgia		
	Value (U.S. \$ Million)	Volume (Million Units)
Cyclobenzaprine	10.0	48.3
Other muscle relaxants	18.5	89.8
Total muscle relaxants	28.5	138.1

Source: Frost & Sullivan analysis.

Cyclobenzaprine Use and Dosing

- Cyclobenzaprine is used primarily for the treatment of flares.
- Due to its sedative effects, it is used most often at bedtime.
 - However, depending on pain levels, some physicians may prescribe it for daytime use if the patient can manage the possible drowsiness.
- Dosing ranged from 5 mg to 10 mg at bedtime to 20 mg, including a daytime dose.
- One physician reported using cyclobenzaprine for chronic treatment (6 to 12 months) using a 5 mg dose at bedtime. However, most physicians used it episodically, typically for 3 to 4 weeks at a time or until the flare subsided.
- Cyclobenzaprine is used mostly in combination with other drugs, especially antidepressants, but occasionally as monotherapy.
- Only 3 out of 12 of the physicians surveyed did not use cyclobenzaprine at all. The main reasons given for not using it were its adverse effects, including:
 - Dry mouth, which can lead to gum disease
 - Blurred vision
 - Urinary retention
 - QTc prolongation, which may require additional medication
 - Complicates cognitive problems (“fibro fog”)

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Competition

- Extensive secondary research, as well as interviews with physicians, have not identified any new drugs currently being tested specifically for fibromyalgia. The FDA recently rejected Jazz Pharmaceuticals' NDA for sodium oxybate (Rekinla®). While the FDA showed no reservations towards its efficacy for the treatment of FMS, concerns related to drug abuse and control were raised. The company has indicated that it may conduct further studies and provide a new risk evaluation and mitigation strategy (REMS) for their product. At this point, it is uncertain whether Rekinla will obtain FDA approval in the forecast period considered for this study.
- However, there are a number of drugs currently in clinical trials for pain indications, and it is possible that some of them may eventually compete for off-label use in fibromyalgia. Although the field is already crowded with off-label drugs, the success of Lyrica is ample evidence that any of these drugs that goes on to achieve a label indication for fibromyalgia can potentially look forward to substantial sales (as can TNX-102).
- The real competition comes from the drugs currently available. Besides Lyrica, there are a significant number of drugs being used off label, including both generic cyclobenzaprine and Amrix®, Cephalon's extended release formulation. Due to the price sensitivity of large parts of the market, generic drugs, in particular, will provide significant competition for TNX-102 and slow its acceptance by physicians.

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Conclusions

- The expression of fibromyalgia symptoms in individual patients is almost as varied as the treatment regimens physicians use in dealing with them. In the absence of knowledge of the underlying cause of the disease, the only option is to attempt to ameliorate the symptoms, often with a combination of drugs and lifestyle changes. FMS rarely resolves completely, either spontaneously or with treatment. The goal of treatment; therefore, is not eradication of the disease, but management of the symptoms to allow the patient to experience increased energy and the ability to undertake the normal activities of daily life. In fact, some physicians use this as the indicator of successful treatment, instead of or in addition to a reduction in pain or other symptoms.
- There are important differences in the approaches taken by primary care physicians and specialists in the treatment of fibromyalgia. PCPs use substantially more muscle relaxants, including cyclobenzaprine, than specialists providing secondary and tertiary care. They are also more aware of the economic stress of many of their patients and more concerned about cost and insurance coverage as significant barriers to the adoption of any new drug, not only TNX-102.
- The unmet need in fibromyalgia treatment is high, and there is a significant opportunity for a reformulated product, such as TNX-102, to find a place in the physician's armamentarium if it can be shown to be more effective or more tolerable than what is currently available.

Recommendations

- The major market segment for TNX-102 appears to be primary care physicians, rather than specialists in secondary and tertiary care. This has significant implications not only for TONIX's marketing strategy, but also for its corporate development. Marketing to the ~118,000 general and family practice physicians in the United States will require far more resources than marketing to ~1,400 pain specialists. TONIX should strongly consider seeking a partner that has the resources necessary for this task.
- TONIX's proposed strategy of marketing TNX-102 for the treatment of flares is in good accord with the current usage of generic cyclobenzaprine. If it could be shown that the new formulation allowed longer term use due to a reduction in side effects, that would provide a significant product differentiation from generic cyclobenzaprine, which is largely restricted to episodic use for a few weeks at a time.
- Physician education about the advantages of TNX-102's pharmacokinetics profile will also be important.
- Finally, we recommend undertaking a larger study at a later time in the development of this product in order to reaffirm findings when extending those to entire U.S. population of physicians treating fibromyalgia.

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Appendix – Initial Product Profile

	Efficacy	Safety	Utility	Economics
Product A	<p>30-40% pain reduction</p> <p>30% fatigue, sleep, mood improvement</p> <p>Return to pre-flare baseline for fatigue, sleep, and mood</p> <p>Robust treatment durability</p>	<p>Less than 5% somnolence</p> <p>Pregnancy B</p>	<p>Few precautions</p> <p>Few DDI</p> <p>QD/bedtime compliance</p>	<p>Reduces concurrent drug dosages</p> <p>Eliminates need for some concurrent drugs</p> <p>Widespread Improvement QOL/function</p>
Product B	<p>40% or more pain reduction</p> <p>No disease flares while under treatment</p> <p>Disease modifier</p>	<p>No somnolence</p> <p>Pregnancy B</p>	<p>Few precautions</p> <p>Few DDI</p> <p>QD/bedtime compliance</p>	<p>Eliminates need for concurrent drugs</p> <p>Restores QOL/function</p>

Notes:

DDI = drug-drug interactions

Fewer Precautions with Products A&B when compared to Lyrica, Cymbalta, and Savella: no suicidality/mood changes risk in label, no weight gain, no abuse potential

Fewer DDIs with Products A&B: no interaction with NSAIDs that increase the risk of PUBs, ACE inhibitors, or thioridazine as compared to 3 approved products.

Source: Frost & Sullivan.

Appendix – Revised Product Profile

	Efficacy	Safety	Utility	Economics
Product A	<p>30-40% pain reduction</p> <p>30% fatigue, sleep, mood improvement</p> <p>Return to pre-flare baseline for fatigue, sleep, and mood after 3 weeks of treatment</p> <p>Robust treatment durability</p>	<p>Less than 5% somnolence</p> <p>Pregnancy B</p>	<p>Few precautions</p> <p>Few DDI</p> <p>QD/bedtime compliance</p>	<p>Reduces concurrent drug dosages</p> <p>Eliminates need for some concurrent drugs</p> <p>Widespread Improvement QOL/function</p>
Product B	<p>40% or more pain reduction</p> <p>Greatly reduced frequency or no disease flares while under chronic treatment</p>	<p>No somnolence</p> <p>Pregnancy B</p>	<p>Few precautions</p> <p>Few DDI</p> <p>QD/bedtime compliance</p>	<p>Eliminates need for concurrent drugs</p> <p>Restores QOL/function</p>

Notes:

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Source: Frost & Sullivan.

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Contact Information

Healthcare Group:

Maik Klasen, PhD

Sr. Director

Healthcare & Life Sciences Consulting

Ph: 650.475.4505

Fax: 650.475.1570

Email: Maik.Klasen@frost.com

Steven Hochhauser, PhD, MBA

Senior Consultant

Healthcare & Life Sciences Consulting

Ph: 650.475.6534

Fax: 650.475.1570

Email: Steven.Hochhauser@frost.com

Mariana Kura, MBA

Consultant

Healthcare & Life Sciences Consulting

Ph: 210.678.3662

Fax: 650.475.1570

Email: Mariana.Kura@frost.com