

CENTRAL NERVOUS SYSTEM (CNS) PHARMACEUTICALS (212)

Revenues (\$, millions)	2000	2001	2002	CGR%
Worldwide	49,800	57,300	65,900	15
Antidepressant, anti-anxiety	21,900	25,200	29,000	15
Antipsychotic	9,000	11,300	14,100	25
Anti-epileptic	7,000	8,400	10,000	20
Anti-migraine	3,000	3,400	3,700	12
Anti-Parkinson	2,000	2,200	2,400	10
Other	6,900	6,800	6,700	-1

Class Definition: This class includes prescription drugs used to treat mental disorders (depression, anxiety, psychoses, others), or diseases/disorders of the central nervous system (epilepsy, migraine, nausea & vomiting, Parkinson's disease, stroke, Alzheimers, others). Drugs used to treat pain are not included here, but are covered separately.

Outlook

This market addresses disorders that affect many millions of people. In the U.S. alone, more than 460 million prescriptions were dispensed for treatment of these illnesses during 2001 and many, if not most, of these therapies have significant drawbacks or side-effects associated with their use, leaving the door open for major market expansion with improved, innovative therapies.

Approximately 20 million individuals with an anxiety disorder such as panic, social anxiety disorder, agoraphobia, obsessive compulsive disorder or generalized anxiety seek medical help annually for their problem. Another group, estimated to number 15 million or more, includes those individuals who suffer from anxiety that is severe enough to impact their ability to function but who do not seek or receive medical treatment. It is important to note that much of the treatment of anxiety disorders is with products that are considered to be first and foremost ‘antidepressant’ medications. Because many of the newer medications work equally well in both depression and anxiety states and these disorders so often co-exist, the differential diagnosis is often blurred between them.

None of the other disorders in this CNS category is believed to be quite so pervasive as the anxiety disorders, but several represent major medical and emotional problems. Mood disorders such as unipolar and bipolar depression affect an estimated 25-30 million in the U.S.; 25 million suffer with chronic sleep disorders such as insomnia, sleep apnea and narcolepsy; eating disorders such as anorexia, bulimia and obesity affect approximately 20 million; and periodic migraines affect an estimated 20 million sufferers.

Some other diseases included here have a much lower incidence, but take a terrible toll in lost productivity and quality of life. These include Alzheimer's which is estimated to currently affect about 5 million in the U.S., anticipated to increase to nearly 7 million during this first decade of the 21st century; schizophrenia and bipolar disorder, diseases that usually strike young adults and most often follow a chronic course, that affect about 3 million each; epilepsy, with about 2 million sufferers; Parkinson's disease that affects about 1.5 million; and some others such as multiple sclerosis, Huntington's and ALS that impact the lives of patients and their families numbering in the hundreds of thousands.

Anxiety Disorders

Generalized anxiety disorder and panic disorder including agoraphobia are two of the major illnesses treated with the anxiolytics. The chronicity and pervasiveness of anxiety disorders form the basis for the anxiolytics finishing 2001 with estimated U.S. sales of over \$1.5 billion. More than 80 million prescriptions were dispensed in this category. More than 80% were for benzodiazepines, products that are recognized to have potential for abuse and dependence and to cause withdrawal symptoms.

The dollar value of this market segment would be much larger if it were not for the large proportion of generics prescribed.

Despite their drawbacks, benzodiazepine anxiolytic products have continued to do quite well. Upjohn's Xanax®, a major anxiolytic in the U.S., with peak sales of nearly \$600 million annually prior to generic competition in the mid-1990's, now sells about \$120 million. And, even after numerous years of generic competition, two other leaders in the category, Ativan® and Valium®, are selling at the \$90 million and \$60 million levels respectively. Generic versions of these brands continue to erode the dollar value of this segment, but at more than 66 million dispensed, prescriptions for benzodiazepines are at an all time high. There is some suggestion that once an anxiety patient has been treated for any significant period with a benzodiazepine, that patient perceives little or no benefit from treatment with a non-benzodiazepine anxiolytic.

BuSpar®, Bristol-Myers Squibb's non-benzodiazepine anxiolytic introduced in the mid-1980's, was heralded for its lack of abuse potential or withdrawal symptoms. At its peak, BuSpar® delivered annual sales of more than \$750 million annually. The patent-protection actions taken by BMS had been effective through the year 2000, but beginning in the 2nd quarter of 2001 generic competition significantly eroded BuSpar® sales and sales for 2001 dropped to below \$450 million. Buspirone, the active ingredient in BuSpar® and its generics remain a

preferred anxiolytic for use in patients who are believed to already have problems with substance abuse. One other non-benzodiazepine, non-SSRI, anxiolytic under development is pagoclone, by Pfizer. It is currently in Phase III for panic disorder, along with another Pfizer asset, pregabalin (Lyrica®), the follow-on to Neurontin®, that is being developed for several anxiety disorders and bipolar disorder. Deramciclone, a 5HT₂ receptor antagonist from Pharmacia and NGD91-3, a Neurogen/Pfizer collaboration are both in Phase II being developed for generalized anxiety disorder. Other compounds in Phase II for anxiety disorders include: ANPH 102 from Ancile Pharmaceuticals; GABA-A α_2/α_3 Agonist from Merck; R673 from Roche ; NAD299 from Astra Zeneca; SR46349 from Sanofi-Synthelabo and siramesine from Forest Labs.

Short-acting benzodiazepines are also used extensively to relax and relieve anxiety prior to surgical procedures. The largest of these is Versed® which had peak year sales of nearly \$400 million in 1999. Generic competition for Versed® first hit the market in mid-2000. Since this is almost exclusively an injectable product, sales of the brand eroded quite quickly and finished 2001 down about 80% versus 2000 at around \$40 million. Abbott, Baxter, ESI Lederle and some others with strong positions in the marketing of injectables have garnered the largest shares of the generic midazolam market.

The trend toward new indications for several of the SSRI and SNRI antidepressants in the treatment of anxiety-type states such as panic, social anxiety disorder, generalized anxiety disorder (GAD) and post-traumatic stress disorder has led to their increased use as anxiolytics. Obsessive Compulsive Disorder (OCD) and disorders of impulse control are other disorders grouped with the "anxiety states". Fluvoxamine (Luvox®), a non-benzodiazepine, SSRI-type product from Solvay was approved for treatment of adult OCD in late 1994, pediatric OCD in early 1997, and sold over \$200 million during 2000. Sales have declined by 50% to about \$100 million in 2001 due to generic

competition. Similarly, Effexor XR®, Prozac®, Paxil®, and Zoloft®, SNRI/SSRI-type antidepressants, have been approved for various anti-anxiety indications such as OCD, panic disorder, post-traumatic stress disorder; social anxiety disorder and generalized anxiety disorder. As this type of antidepressant receives more use in these anxiety states the lines between treatment of anxiety and depression will become ever less clear.

Depression

Depression, often a chronic disorder, is estimated to affect 25 to 30 million people in the U.S. alone. Nearly 175 million antidepressant product prescriptions were dispensed in 2001 (some significant portion for treatment of the anxiety states discussed above) and sales of these agents have now exceeded the \$12 billion level. Until the late 1980's, the available selection of antidepressant drugs produced side-effects that limited most non-specialists' use of these agents. The introduction of Prozac® in early 1988 has dramatically expanded the use of antidepressants by primary care clinicians since it (and other SSRIs) is relatively free of many of the side-effects associated with the older products. Despite the advent of generic competition in the second half of 2001, Prozac® had U.S. sales in excess of \$2 billion for the year. Major generic inroads in 2002 may reduce those sales dramatically.

The introduction of newer "Prozac®-like" antidepressants, e.g. sertraline (Zoloft®) by Pfizer in early 1992 and paroxetine (Paxil®) by SmithKline Beecham in early 1993, with profiles as "cleaner, more specific, less toxic agents" compared to the older tricyclic antidepressants such as Elavil® and Tofranil®, etc. has further expanded this market. Both Zoloft® and Paxil® had U.S. sales approximating \$2¼ billion in 2001. Wyeth's venlafaxine (Effexor®), a structurally novel antidepressant which inhibits reuptake of both serotonin and norepinephrine, was introduced in early 1994 and it along with Effexor® XR garnered \$1¼

billion in 2001 sales to provide even further market expansion. In mid-1998, Forest marketed its citalopram (Celexa®) and, despite its late entry in the SSRI market, it's sales were in excess of \$1 billion for 2001. Two other newer agents, Bristol-Myers Squibb's nefazodone (Serzone®) and Organon's mirtazapine (Remeron®) delivered sales of nearly \$400 million and nearly \$450 million respectively for 2001 and continue to fuel the ongoing expansion of this market.

Several other factors have or will have an impact on the almost dizzying expansion of this market segment. In 3rd quarter 2000, Lilly introduced fluoxetine under the brand name Sarafem® for the treatment of PMDD (premenstrual dysphoric disorder) and this brand delivered more than \$90 million for 2001. In an effort to stem brand erosion from generics, Lilly has also introduced a "once-weekly" dosage for Prozac® this year and partial year sales exceeded \$50 million. Lilly is also studying fluoxetine for dysthymia, a milder form of depression and a combination of fluoxetine and olanzapine for psychotic depression. Paxil® CR from Glaxo is also in Phase III for premenstrual dysphoric disorder.

There are several new antidepressants awaiting FDA approval or in late-stage development. Pharmacia's reboxetine (Vestra®), is looking for approval in 2002 with evidence of efficacy even in severely depressed patients, while Forest's escitalopram (Lexapro®), a follow-on to Celexa®, is anticipating approval in mid-2002. Others awaiting FDA review include: Ariza®, gepirone, from Organon and Cymbalta®, duloxetine, from Lilly.

Those in late stage development include: CP-122,721, an NK1 receptor antagonist, and sunepitron for anxiety and depression, both from Pfizer; aprepitant, a substance P antagonist from Merck for the treatment of depression and chemo-induced emesis; BTS-74398, a 5HT reuptake inhibitor for depression and Parkinson disease, and TAK-637, an NK1 receptor antagonist, both from

Abbott; DU125530, a 5HT_{1A} receptor antagonist for depression, from Solvay; fibanserin or flibanserin from Boehringer Ingelheim for depression; NAD299 for depression and anxiety from AstraZeneca; Org 12962, a 5HT_{2C} receptor agonist, and Org 34517, a glucocorticoid receptor antagonist, both from Organon for depression; R673, a G-protein coupled receptor modulator from Roche for depression; and SR 48968 and SR 58611, from Sanofi-Synthelabo for depression and anxiety and for severe depression respectively.

Growth in this market segment will continue as many of the currently marketed products expand their use into treatment of panic, obsessive-compulsive disorder, generalized anxiety disorder, post-traumatic stress disorder, social anxiety disorder, eating disorders including anorexia and bulimia, and premenstrual dysphoric disorder. Some have also gone on to get maintenance claims in these indications. And while a few products have indications for use in multiple indications, several other similar products are also being used without benefit of FDA approved indications. As mentioned earlier, a downside for this market is, and will continue to be the advent of generics of some of these SSRI's. Luvox®, used mostly for anxiety disorders, saw its first generic competition late in 2000 and saw a reduction in sales of about \$100 million. Generic competition for Prozac® came early in the second half of this year and probably reduced Prozac® revenue by as much as \$600 million. Future year losses for these two brands will be even greater. Among the other key brands, only Forest's Celexa® is likely to see generic competition in the near term.

There continues to be a widespread initiative to increase awareness and recognition of depression both in the community and among young people through programs held on the college campus. A broad effort is also underway to de-stigmatize the treatment of mood disorders, especially depression, in the

hope of bringing more individuals into treatment through their primary care physicians earlier in the course of depressive illness. The co-morbidity of cardiovascular disease and depression is also receiving much greater recognition. As a result, more physicians are inquiring about issues of mental and emotional well-being during regular office visits and more and more individuals are acknowledging the symptoms that can aid physicians in their diagnosis of depression and other mood and anxiety disorders. All of these forces have combined to make the category of antidepressants the single largest segment of the central nervous system pharmaceuticals based on revenues.

Sleep Disorders

The vast majority of the 25 million individuals suffering with chronic sleep disorders have difficulty either in initiating sleep when they go to bed or have difficulty getting back to sleep after awakening during the night. Therefore, the major market opportunities are associated with achieving and maintaining sleep.

It is estimated that only about 4-5% of the U.S. population or about 10-14 million people have taken a "sedative-hypnotic" sleep-promoting prescription drug during the last year and about one-half that many have taken a non-prescription sleep medication. A large portion of these prescription drugs are benzodiazepines with all of the risks discussed earlier. Treatment of sleep disorders also comes from outside the "sedative" class. Up to 10% of the use of several of the benzodiazepine products marketed as anxiolytics is to "promote sleep" and a similar percentage of some of the older, non-SSRI antidepressants is prescribed to improve sleep. Combining these market segments suggests that the total market for sleep promotion and maintenance is in excess of \$1½ billion.

Ambien®, zolpidem originally from Searle via an agreement with Lorex, and now

marketed by Pharmacia, received FDA approval in December, 1992 and delivered 2001 sales of nearly \$1 billion. Ambien® seems to have much less potential to cause dependence or to produce rebound insomnia on withdrawal compared to the benzodiazepines. It appears that more and more physicians are prescribing it for more patients and for more extended periods. Sanofi-Synthelabo actually owns the rights to Ambien® and will take over the marketing of this blockbuster in 2002. It will be interesting to see how Ambien® fares following this transition. It's patent protection appears to continue into 2006. A flash-dose zolpidem from Biovail is awaiting FDA review.

Sonata®, zaleplon, is a Wyeth product that is a short-acting, non-benzodiazepine, GABA agonist hypnotic. It was approved and marketed in late 1999. This new agent was touted as causing no post-dose hangover or memory impairment. Accordingly, it can be taken on an as-needed basis. However, despite strong promotion in 1999 at introduction and through 2000, Sonata® delivered sales of less than \$100 million during 2001, up just marginally over 2000. Elan will participate in the marketing of Sonata® beginning sometime in 2002 and perhaps with that added marketing effort the product will see some renewed growth in the future. Another agent that is in Phase III for treatment of insomnia is zopiclone (Estorra®) from Sepracor. In Phase II development there is a compound from Neurocrine Biosciences known as NBI34060-MR for primary insomnia with sleep maintenance complaints.

In a much smaller segment of the sleep disorder market, treatment of narcolepsy, Cephalon has licensed exclusive rights to develop, market and sell modafinil (Provigil®), a central α -adrenergic agonist for the treatment of individuals with the "sleep attacks" and daytime drowsiness associated with narcolepsy. There are some data suggesting that modafinil might also have

utility in the treatment of Alzheimer's. Cephalon received approval with orphan drug status for modafinil in the treatment of narcolepsy and excessive daytime sleepiness in late 1998. During 1999, its first year on the market, Provigil® delivered sales in excess of \$25 million and grew to over \$130 million in 2001. Provigil® is also being studied in Alzheimer disease, Parkinson disease, and for fatigue associated with multiple sclerosis. A much smaller potential product, Xyrem®, sodium oxybate from Orphan Medical, currently awaits FDA review with approval anticipated in the second half of 2002.

Eating Disorders

Eating disorders represent a market segment that had been virtually without safe, approved medication available for chronic treatment. An estimated 20 million or more severely overweight or obese adults in the U.S. represent a major market opportunity for a safe, effective treatment, but the largest opportunity for a safe anti-obesity medication would come from the group of an estimated 80 to 100 million adults who are just marginally over acceptable weight but who are constantly "battling the bulge". Interest in the treatment of obesity with a combination of phentermine and fenfluramine coupled with the introduction of Interneuron Pharmaceuticals' dexfenfluramine, marketed by Wyeth as Redux®, resulted in a significant increase in the prescribing of antiobesity agents during 1996 with a nearly 200% increase to approximately \$500 million in sales of antiobesity agents for 1996 versus 1995. Sales continued to increase throughout the first half of 1997, but then plummeted when Redux® and Pondimin® were withdrawn from the market by Wyeth in the fall of 1997.

Redux® had earlier shown some limited liability for causing primary pulmonary hypertension, a condition that while rare, carries a significant 4-year mortality. However, it was the potential for causing cardiovascular problems related to valvular heart disease that precipitated the

withdrawals of Redux® and Pondimin®. In the wake of these withdrawals, the antiobesity market for 1997 declined about \$100 million from 1996 levels.

Despite concerns regarding potential side-effects with Redux®, another new, somewhat similar, anti-obesity product, sibutramine (Meridia®) from BASF's Knoll Pharmaceuticals [now owned by Abbott], was marketed in early 1998. Unlike Redux®, Meridia®, sibutramine, is an SNRI (serotonin-norepinephrine reuptake inhibitor). Meridia® does not increase release of serotonin, does not seem to be likely to cause primary pulmonary hypertension, but does show the potential for causing a basic hypertension. Meridia® 1998 U.S. sales exceeded \$100 million, declined somewhat in 1999 and 2000 and have now recovered and grown to about \$130 million for 2001. Some of the earlier decline was due to the April, 1999 introduction of orlistat (Xenical®) by Roche. Abbott now anticipates long-term use studies that will show Meridia®'s benefits among patients with cardiovascular/diabetic problems and plans a more medically focused marketing effort that highlights the medical problem of obesity.

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Xenical® is a unique, non-stimulating product for the treatment of obesity that works by inhibiting pancreatic lipase and therefore results in a reduction of the absorption of fats from the intestinal tract. Unlike the centrally acting, stimulant-type antiobesity agents, Xenical® tends to produce a minimal number of side-effects and these tend to be related to bowel discomfort and bowel urgency and frequency. This product has also been shown to offer the added benefit of reducing the total level of blood lipids by about 10%, thereby potentially providing a secondary benefit to obese patients in addition to weight loss. Roche intends to ultimately earn labeling for Xenical® that will support long term therapy. While Meridia® had helped the anti-obesity market recover from its 1997 losses, the 1999 introduction of Xenical® caused some

modest expansion of the anti-obesity market with U. S. sales of nearly \$150 million in its shortened first year, further growth to more than \$180 million in 2000, but then a decline to \$170 million for 2001. Worldwide sales of Xenical® grew marginally in 2001 to over \$550 million. There is some concern that Xenical® use may reduce the absorption of key vitamins and minerals, though this concern is theoretical at this time. If, following post-marketing surveillance studies, Xenical® is shown to be relatively safe and free of abuse potential, and patients find its side-effects to be tolerable, Xenical® can be expected to bring about further market growth and expansion. Roche has withdrawn its sNDA for an indication for Xenical® in the treatment of patients with type-2 diabetics for improvement of glycemic control, but instead hopes to incorporate the diabetes clinical data into current Xenical® labeling.

Topamax®, topiramate, from J&J is currently marketed as an anticonvulsant but has shown a unique capability among that class of medications to cause weight loss. Since many patients refuse treatment or are non-compliant with medication in illnesses such as seizures, bipolar disorder, migraine and others where Topamax® may have some utility, it is likely that it will get a large share of the early trials because of its weight loss characteristic.

Two compounds in Phase III for treatment of obesity are Sanofi-Synthelabo's SR141716, listed as a central cannabinoid receptor antagonist, and Axokine, a ciliary neurotrophic factor from Regeneron and Proctor & Gamble. Aventis, Glaxo SmithKline, Pfizer, Restoragen and Amgen each have compounds in Phase II development for the treatment of obesity

Anticonvulsants

Anticonvulsants include a group of products that are used not only in the treatment of epilepsy, but these products are increasingly being used as sole or adjunctive treatment in anxiety states, mood disorders, migraine,

personality disorders, disorders of aggression and impulse control and in schizophrenia. As a group, these products account for revenues in excess of \$4½ billion and prescriptions numbering nearly 60 million. Overall, the anticonvulsant market is currently about one third the size of the antidepressant market in both dollars and prescriptions. Abbott's Depakote®, Roche's Klonopin®, Novartis' Tegretol® and Trileptal®, Pfizer's Neurontin®, Glaxo's Lamictal® and J&J's Topamax® have seen major growth come from use in the treatment of patients with manic-depression or bipolar disorder and other psychiatric illnesses, especially those with a component of impulsivity.

Pfizer's gabapentin (Neurontin®) is one major example of an anticonvulsant that is generally used outside of its labeled indications. Neurontin® was marketed in early 1994 and is now selling over \$1.7 billion annually in the U.S. despite its limited indication of adjunctive therapy for treatment of partial seizures in adults. Neurontin® has been unsuccessfully studied for use in several psychiatric disorders, as well as in neuropathic pain and post-herpetic neuralgia. However, an estimated 90% of its use is outside of epilepsy. At this point it is probably most frequently used to provide pain relief in neuritis and neuropathy and to control symptoms of anxiety and agitation in bipolar patients. Because of patent issues associated with Neurontin® and other issues related to half-life and dosing frequency, Pfizer is not focused on further development of Neurontin®, but is developing a follow-on compound known as pregabalin (Lyrica®) for use in indications where Neurontin® is perceived to show significant utility.

Depakote®, another multi-faceted anticonvulsant, was initially marketed for use in seizure disorders in the mid-1970's. It was approved for acute treatment of mania in mid-1995 and for preventative treatment of migraine headache shortly thereafter. It is likely that 75% of the total of more than \$1 billion in Depakote® 2001 U.S. sales came from use in psychiatric disorders.

Klonopin® (clonazepam), is a benzodiazepine with a long half-life that was initially labeled only as an anticonvulsant but has been used predominantly in psychiatric disorders for many years. Klonopin® received FDA approval for treatment of panic disorder during 1997. Klonopin® delivered sales of more than \$50 million in 2001, despite having generic competition since 1996.

Another anticonvulsant initially indicated for adjunctive therapy, Glaxo's lamotrigine (Lamictal®), reached the U.S. market in early 1995. This product carries broader labeling outside the U.S. An NDA for monotherapy in epilepsy was approved by FDA in late 1998. Lamictal® labeling includes a black box warning regarding incidence of serious rash. Despite this limitation, 2001 annual sales surpassed the \$320 million mark. Current clinical programs indicate that emphasis is being placed on broadening indications to include treatment of depressed patients and for maintenance treatment in bipolar disorder.

Topamax® (topiramate) from J&J received FDA approval in December, 1996 also as adjunctive therapy, and was introduced in early 1997 delivering sales of about \$25 million during that shortened first year. 2001 sales of Topamax® showed strong growth to over \$400 million. Unlike most other anticonvulsants, Topamax® tends to cause weight loss rather than weight gain and this may foster additional growth in the future as this characteristic becomes better appreciated. Topamax® is currently being studied for use in adults as monotherapy in epilepsy as well as in migraine and bipolar disorder.

Other new anticonvulsants include: Gabitril® (tiagabine) marketed by Cephalon, licensed from Novo Nordisk, for adjunctive therapy for partial seizures which cleared FDA in late September, 1997 and sold about \$20 million in 2001; Trileptal® (oxcarbazepine) from Novartis, approved and marketed in early 2000 for partial seizures as adjunctive or monotherapy in adults and as

adjunctive therapy in children which delivered over \$100 million in its first full year; and, Keppra® (levetiracetam) from UCB Pharma for adjunctive therapy in adults with partial onset seizures with epilepsy, introduced in early 2nd quarter 2000 and delivering sales of nearly \$90 million in 2001, its first full year.

One additional new anticonvulsant, zonisamide (Zonegran®) from Dainippon that is already marketed in Japan for refractory epilepsy received FDA approval in late March 2000 for adjunctive treatment of partial seizures in adults with epilepsy. It is being marketed in the U.S. by Elan, and following its 2nd quarter 2000 introduction it delivered 2001 sales of about \$30 million.

In late 1997, Elan launched Diastat®, a rectal gel formulation of diazepam, through its Athena Neuro-sciences, to deal with acute seizure activity while avoiding a visit to the emergency room. This product, now marketed by Xcel Pharmaceuticals, allows the home caregiver to provide a treatment that can interrupt acute repetitive seizures. While this product will probably not be a major player (about \$20 million in 2001), it will be highly valued by the neurologists and their patients who will feel as if they now have some ability to control acute seizure activity in the home setting. Another new formulation of an old drug, Carbatrol®, an extended-release, sprinkle capsule form of carbamazepine from Shire Pharmaceuticals, labeled for epilepsy and pain of trigeminal neuralgia, was launched in the first quarter of 1998, delivered sales of nearly \$50 million for 2001 and is currently being studied in bipolar disorder.

Anticonvulsants in latter stage development are: pregabalin (Lyrica®) the follow-on compound to Neurontin® in Phase III from Pfizer for epilepsy, Alzheimer's, bipolar disorder, diabetic neuropathy, panic disorder, GAD and social phobia; Xilep®, rufinamide, for epilepsy in adults and children aged 2-18 (and for neuropathic pain) and a compound known as TRI 477, for epilepsy both in Phase III from Novartis. In Phase II are harkoseride

for epilepsy from Schwarz Pharma; retigabine for complex partial seizures from Asta Medica; talampal for severe epilepsy not responsive to other drugs, from Lilly; and SB204269 for epilepsy and migraine by GlaxoSmithKline. Lamictal®, already marketed for seizures, is currently being developed for depression and maintenance in bipolar disorder.

Despite the number of new products mentioned above, a significant portion of the near-term expansion of this market is likely to come from the older products because of increased trial of the established anticonvulsants in the treatment of various psychiatric and pain disorders. Longer term, one or more of the agents mentioned above has the potential to replace a significant portion of the current lower-cost Dilantin®/phenytoin use as new patients requiring anticonvulsant therapy are placed on the newer agents. Similarly, once the profiles of the recently marketed Gabitril®, Keppra®, Trileptal® and Sonegran®, are more firmly established, it will be easier to forecast how quickly and to what extent these newer adjunctive therapies will provide major market expansion within their approved indications and then beyond in psychiatric and pain disorders as well.

Antiemetics

The increased use of more potent cytotoxic agents for the treatment of various neoplasms with associated nausea and vomiting made the demand for more effective, safe antiemetics a high priority. Sales in this market segment now exceed \$1.7 billion with dollar growth coming predominantly from the trading up from lower priced, older antiemetics to the newer, more effective, higher priced products.

Zofran®, the first of a new class of serotonin antagonist antiemetics, was launched in an injectable form by Glaxo in the U.S. in early 1991 for use in cancer treatment associated nausea and vomiting. First year Zofran® U.S. sales exceeded \$100 million and second

year sales neared \$225 million despite the injectable-only form and the limited indication. Continued expansion of Zofran® indications and dosage forms including an orally disintegrating tablet introduced in 1999 have supported the continued growth of Zofran®. And despite new competition (see below) sales have grown to nearly \$800 million in 2001.

Further expansion of this U.S. market segment came with the introduction of another serotonin antagonist antiemetic, Kytril® from SmithKline Beecham, introduced in injectable form in early 1994. First year Kytril® sales exceeded \$50 million, and with early 1995 approval of an oral tablet form, usage had continued to expand to over \$200 million in 1999. As part of the requirements for the Glaxo SB merger, Kytril® was divested to Roche. U.S. Kytril® sales have declined to about \$170 million in 2001.

Anzemet®, dolasetron, in I.V. and oral forms for chemotherapy induced nausea and vomiting from Aventis and co-marketed by Abbott to hospitals, was approved in late 1997 and delivered sales of nearly \$240 million in 2001. Anzemet® growth will further broaden this market over the next few years as will the development of new indications for the previously marketed serotonin antagonists. Other compounds in Phase III for chemotherapy-induced emesis include aprepitant, a substance P antagonist from Merck and palonosetron, a 5-HT₃ receptor antagonist from MGI Pharma.

Antipsychotics

The current antipsychotic market stands at nearly \$5½ billion and 24 million Rx's. The current growth spurt began with the introduction in April, 1991 of Sandoz's (now Novartis) very high priced clozapine, (Clozaril®), which is now selling at the \$180 million level, despite generic competitors and strong new atypical antipsychotic competition. The advantage that Clozaril® offers is that it generally does not cause the

unwanted movements or feelings (extrapyramidal symptoms or EPS) seen with virtually all of the older, conventional antipsychotic agents and to some degree even with newer atypical ones. And, it is this group of side effects that most often causes a patient to discontinue medication. Clozaril® does, however, have one major drawback, the potential to cause agranulocytosis, a dangerous blood disorder. So, patients who receive Clozaril® must tolerate frequent blood monitoring.

The newer, atypical antipsychotic agents are thought to influence dopamine more specifically in the part of the brain that causes the psychotic symptoms without altering dopamine in the area that causes movement disorders and feelings of motor restlessness. They are also believed to exert some of their beneficial effects via a serotonin-mediated pathway. These newer antipsychotics exhibit evidence of treatment effects not only on the “positive” symptoms of schizophrenia such as hallucinations and delusions, but also on the “negative” and cognitive symptoms of the disease such as social withdrawal, blunted affect, anhedonia, apathy and difficulty thinking. With fewer of the major liabilities seen with all the older antipsychotics, these newer compounds are revolutionizing symptom management of such diseases as schizophrenia, the senile dementias and treatment of some patients with bipolar disorder, especially those with psychotic episodes.

Following Clozaril®, the next atypical antipsychotic to be marketed was Janssen/J&J's risperidone (Risperdal®). It was introduced in 1994, delivered sales of about \$180 million that year and 2001 sales of more than \$1½ billion. While it clearly offers some evidence of reduced side effects versus the older, more traditional agents, it too, seems to cause movement disorders and motor restlessness when given in higher doses. Therefore, there remained significant demand for further improvements in available therapies and several additional new

products stood ready to meet the perceived need.

The next of these to receive FDA approval was Lilly’s olanzapine (Zyprexa®). It was introduced in October, 1996 and with blockbuster speed had recorded nearly \$70 million in U.S. sales in 1996 and exceeded \$2½ billion in 2001. Zeneca’s quetiapine (Seroquel®) received FDA approval in September, 1997, was marketed in October, 1997, delivered modest sales of about \$20 million by the end of that year and has now grown to over \$700 million in 2001, continuing to grow at a record pace. Many physicians seem to feel that Seroquel®, which offers a variety of dosage strengths, is especially useful in elderly patients who are out of touch with reality and in need of antipsychotic medication.

Pfizer’s Geodon® [previously Zeldox®] (ziprasidone) received a “not-approvable” letter pending additional data that showed ziprasidone to be comparable to other atypical antipsychotics in its potential to cause cardiac arrhythmias. Pfizer refiled the NDA, received approval and marketed Geodon® in March 2001. In its shortened first year, Geodon® sales exceeded \$140 million. Now that this product has reached the marketplace, it will be interesting to see if it is able to capitalize on a unique aspect of its profile in that it seems to be less likely to cause weight gain compared to the other atypicals. An injectable formulation of Geodon® is also under review at this time with approval expected in mid-2002. It is currently anticipated that Geodon® will be the first atypical antipsychotic available in a formulation allowing for intramuscular injection. If and when that occurs, Geodon® will have a distinct advantage over its competitors because it will be available for use in the emergency room and in other crisis settings to initiate therapy and very often if a patient is started on one atypical antipsychotic the tendency is to keep that patient on the same product for maintenance.

Other new products in development or awaiting approval for

schizophrenia/psychosis include: aripiprazole (Abilify®) from Bristol-MyersSquibb/Otsuka currently under FDA review; iloperidone (Zomaril®) from Novartis/Titan, currently in Phase III; Ampalex® (CX-516) from Cortex, Osanetant® (SR142801) from Sanofi-Synthelabo, Abbott’s dopamine 3 receptor antagonist, BSF201640, acquired along with the Knoll acquisition; Novartis’ DAT201, another D3 receptor antagonist; Wyeth’s DAB-452; Organon’s ORG-5222; Organon’s CX-691/ORG-24448 and Solvay’s DU127090, all in Phase II. There are other products in the NDA preparation or review phases that deserve mention. A depot formulation of risperidone (Risperdal® Consta) for treatment of schizophrenia, from Janssen. If this formulation retains the benefits of oral risperidone and can be delivered once or twice a month with a depot injection, it will have a significant advantage over oral products that must be taken daily and it will provide for further market expansion once it becomes available in the 2003-2004 time frame. Janssen has also developed an orally disintegrating tablet of Risperdal® that is pending review. Intramuscular formulations of Pfizer’s Geodon® and Lilly’s Zyprexa® also await FDA review. A long-acting depot formulation of Zyprexa® is currently in Phase II for both schizophrenia and bipolar disorder. A filing for a fixed dose combination of Lilly’s Zyprexa® and Prozac® for use in bipolar disorder is anticipated in 2002. Most of the atypical antipsychotics continue to do studies to expand their indications to include such things as treatment of aggression or psychosis in dementia and use in acute mania. Of the currently marketed antipsychotics, only Zyprexa® already has a claim for use in mania.

Prior to introduction of these atypical antipsychotics, this market had been predominantly a generic market. Introductions of these new, single-source, higher priced agents has caused a major dollar expansion. More clinicians are trading

up to these newer agents that are better tolerated and more patients are likely to remain compliant with such medication regimens. Even prior to the marketing of Zyprexa®, Seroquel®, and Geodon® this market segment had been growing at about 20% per year. Now dollar growth is in the 30-35% per year range. Some of this growth has been fueled by expansion of indications and non-labeled use outside of schizophrenia in mood disorders and psychosis with dementia. Growth among antipsychotics will be likely to continue with the advent of new formulations for these atypicals, the introduction of BMS/Otsuka's aripiprazole projected for late 2002 and one or more of these additional new agents making its way into the marketplace.

Alzheimer's Disease

Alzheimer's disease, a neurodegenerative brain disorder that affects the brains' ability to utilize choline, typically leads to progressive memory loss, dementia and death. It is the fourth leading cause of death in the U.S. and is estimated to affect nearly five million older Americans. While antipsychotic agents are often used to treat some of the symptoms experienced by patients with senile dementia brought on by Alzheimer's disease or other causes, only one product, Cognex® initially from Warner Lambert (now marketed by First Horizon Pharm.), had been marketed in the U.S. prior to 1997 with an indication for the treatment of symptoms of Alzheimer's. A second product in this category, Aricept®, donepezil from Eisai, and co-marketed by Pfizer, was launched in early 1997. Both of these two products treat the memory/cognitive impairment that is often the earliest sign of Alzheimer's disease; none has been marketed to stop the disease's progression. Thus, the development of agents to treat many of the symptoms of Alzheimer's or to alter the ultimate course of the disease represent major opportunities in the CNS market.

Development of tacrine (Cognex®) for symptoms of Alzheimer's received much publicity prior to its approval in October 1993. The major concern that slowed final approval was the incidence of elevated liver enzymes seen in some of the elderly patients receiving tacrine in clinical studies. Cognex® completed 1995 with sales of \$55 million and following the new competition from Aricept® in 1997, sales dropped to \$2 million by 2001. In contrast, Aricept, supported by Pfizer marketing muscle, delivered sales of more than \$150 million during its first year and nearly \$600 million in 2001 despite the marketing of additional new agents as discussed below.

In April 2000, FDA approved Novartis' rivastigmine (Exelon®) for treatment of mild to moderate dementia of the Alzheimer's type. Sales in its first shortened year were over \$40 million and these increased to nearly \$150 million for 2001. The continuing growth of Aricept® despite the introduction of Exelon® in 2000 may in part be due to the dosing advantage that Aricept® holds with its once-a-day dosing compared to Exelon® which must be taken twice each day. Novartis' is currently in Phase II with Exelon® TDS, an additional formulation that may improve the product's competitive position. Exelon® carries a bold warning regarding gastrointestinal side effects. Studies are now being planned to compare Exelon® and Aricept® head-to-head. These probably won't be completed until late 2002 or thereafter.

One additional new agent, galantamine (Reminyl®), developed by Shire and marketed by Janssen, was launched in mid-year for mild to moderate dementia of the Alzheimer's type. Thus far, it seems to have had a slow start with sales in the \$30 million range for its shortened first year. Like Exelon®, Reminyl® requires twice-a-day dosing and may be somewhat at a disadvantage to once-a-day Aricept®. Janssen anticipates several additional studies that will help to differentiate Reminyl® from the other products in this category. If they

are supportive, these studies could provide the basis for major Reminyl® growth.

There are other agents at various stages of development: Forest Labs. memantine for mild to moderate Alzheimer's has completed Phase III; acetyl-l-carnitine (Alcar®) for early-onset Alzheimer's from Sigma-Tau Pharm continues in Phase III as does Neotrofin® (leteprenim potassium) a glutamate receptor antagonist from NeoOncoRx; Cortex' Ampalex® (CX516) in Phase II for Alzheimer's and for cognitive dysfunction associated with schizophrenia and Pfizer/Albany Molecular Research's CI-1017 for Alzheimer's in Phase II. . At least two statins are also being developed in Phase II for the treatment of Alzheimer's: Altacor®, lovastatin from Aura Labs (Merck's Mevorcor® was off patent as of mid-2001); and Lipitor® from Pfizer. NS2330, a dopamine uptake inhibitor from Boehringer Ingelheim; NGD 97-1, a gamma-aminobutyric acid agonist from Pfizer/Neurogen; Phenserine, a acetylcholinesterase inhibitor from Axonyx; rasagiline mesylate, an irreversible MAO-B inhibitor from Teva; S8510, a benzodiazepine partial inverse agonist from GlaxoSmithKline; SR57746 from Sanofi-Synthelabo; and SL65.0102, a 5-HT4 partial agonist also from Sanofi-Synthelabo are all in Phase II development for treatment of Alzheimer's. Marinol®, dronabinol, is also in Phase II from Roxanne and Unimed – intended to reduce the disturbed behavior caused by Alzheimer's.

A significant body of work has now been developed by Wyeth in a National Institute on Aging-sponsored trial showing that estrogen replacement therapy in women seems to reduce the potential risk of developing Alzheimer's and/or for suffering its negative effects. This work is now in Phase III and within the next two years Wyeth may seek an indication for Premarin® for the prevention of cognitive function loss associated with Alzheimer's in women. Similarly, Pfizer and Merck are doing trials with Celebrex® and Vioxx®, their non-

steroidal antiinflammatory drugs, for the treatment or prevention of Alzheimer's. If any or all of these studies provide positive results and gain approval, the use of these agents as preventative medicine in Alzheimer's will accelerate dramatically.

Because there are some dementias that, unlike Alzheimer's, are reversible with appropriate treatment, it would be very helpful if Alzheimer's and the other dementias could be differentiated through simple, accurate diagnostic methods. Today that is another strong area of ongoing research. Two neuroscience companies that have collaborations ongoing with major players in the pharmaceutical industry relative to the development of curative treatments and/or diagnosis of Alzheimer's and other neurodegenerative diseases of the brain are Neurocrine and Cephalon each with various partners.

Migraine

With an estimated 27 million migraine sufferers in the U.S. alone, the need for effective treatment of migraine is clear. Over a relatively short period of nine years, this market has grown from about \$250 million to nearly \$1¾ billion. Until the early 1990's, there were very few treatments to control a migraine once it had begun and most of these had side effects that made many migraine sufferers unable to tolerate them; or, they required a visit to a medical facility for an intravenous or intramuscular injection.

At the close of 1992 FDA approved the first new 'triptan' agent, sumatriptan (Imitrex®), from Glaxo for the treatment of migraine. The initial dosage form approved required subcutaneous injection by the patient at the time the first symptoms of the migraine develop. Only the most highly motivated migraine sufferers are likely to use the injectable formulation. However, that first year U.S. sales of Imitrex® exceeded \$100 million and 1994 sales grew to over \$230

million despite the limitation of its subcutaneous injectable form.

The oral formulation of sumatriptan was approved and marketed during the third quarter of 1995. With the availability of the tablet form, sales expanded dramatically, closing 1995 at more than \$330 million. In 1996, the first full year of tablet availability, Imitrex® sales soared to nearly \$600 million. U.S. sales for Imitrex® have continued to rise and now total more than \$1 billion in 2001 for the product overall. This performance was boosted by Glaxo's September, 1997 addition of the nasal spray formulation of Imitrex®. Glaxo currently is in Phase II with a needle-free injection formulation for Imitrex®.

Until Imitrex®, most patients believed that nothing could be done to control a migraine headache and now these patients are being educated regarding the availability of new, effective therapy in order to maximize market development. Glaxo and others have funded direct to consumer advertising that counsels migraine sufferers to see their physicians for the latest advances in migraine treatment. If Imitrex® sales are any indication of its effectiveness, then the educational program must be working.

And, for those migraine sufferers who cannot tolerate or benefit from Imitrex®, some additional alternatives are now available. In fact, for migraine sufferers, 1998 was a banner year. Novartis' non- 'triptan' product, Migranal®, dihydroergotamine mesylate in a intra-nasal formulation of DHE-45® (an IV/IM injectable product for migraine), was launched in early 1998. It finished 2001 with less than \$10 million in sales. Glaxo, in addition to Imitrex®, received FDA approval of its new 'triptan' migraine product, naratriptan, Amerge®. Glaxo introduced it in March, 1998 and ended 2001 with over \$100 million in sales.

Astra/Zeneca got rights to 'triptan' migraine treatment, zolmitriptan (Zomig®), as part of

the agreement that allowed for the merger of Glaxo and Wellcome. Zomig® was launched in late 1997 and delivered 2001 sales of nearly \$200 million. Merck received mid-1998 approval for a fourth 'triptan' product, rizatriptan (Maxalt®), in a regular tablet and a fast-dissolving dosage form for the treatment of migraine and achieved sales of more than \$220 million in 2001. The fast-dissolving aspect of the Maxalt® Melt formulation offered a particular benefit to those migraine sufferers who experience nausea with their headache. The fast-dissolving formulations require little or no liquid be taken with them making them more easily tolerated compared to those medications that must be taken with fluids. AstraZeneca introduced a rapidly disintegrating version of Zomig® during 2001. This new formulation may help to accelerate growth of the Zomig® brand. Another new addition to this marketplace during 2001 was almotriptan, Axert®, from Pharmacia. It was introduced early in the second half of the year and delivered limited sales of about \$5 million for 2001.

The outlook for future products in this category remains bright for additional 'triptan' products. Frovatriptan (Frova®) is a product coming from Elan with approval anticipated early in 2002. FDA approval of Pfizer's eletriptan (Relpax®) for treatment of acute migraine (already marketed in Europe) is now expected during the first half of 2003. AstraZeneca also has ongoing studies to expand the indications for Zomig® to include use in adolescents age 12 to 18, cluster headache, menstrual migraine prophylaxis and migraine with aura. GSK is also in Phase III seeking an indication for menstrual migraine prophylaxis for Amerge®.

Outside of the 'triptans', Pozen has two compounds in development, MT 100 and MT300 in Phase III for migraine pain. Questcor and Nastech Pharmaceutical are collaborating on Migrastat®, an intranasal formulation of propranolol, also currently in Phase II. Pozen also has a compound known only as MT400 in Phase II for migraine. This compound may be a 'triptan-type' product.

Botox®, the botulinum type A toxin, is another agent being developed for treatment of migraine and chronic tension headaches. This agent is currently in Phase II by Allergan.

With all the new products recently marketed and expected near-term along with the efforts to expand the indications and provide additional formulations for these products, the migraine segment should continue to see expansion and growth.

Parkinson's Disease

The \$650 million market for treatment of Parkinson's disease has been one of the smaller and slower growing of those included among central nervous system pharmaceuticals. An estimated 1.5 million Americans have Parkinson disease. This year dollar sales have surged ahead some due to trading up from the less expensive older or generic products to the newer higher-priced agents. However, prescriptions for this therapy category have been down slightly in each of the last two years suggesting that the new products introduced in the 1997-98 time-frame did not deliver the beneficial, side-effect-free treatment they had hoped and many patients without debilitating symptoms may have stopped therapy as they take a wait and see approach to their disease progression.

During the last half of 1997 and first half of 1998, three new products for the treatment of Parkinson's disease were introduced. They are Pharmacia/Upjohn's pramipexole (Mirapex®), introduced in July, 1997, Glaxo SmithKline's ropinirole (ReQuip®), introduced in December, 1997, and Roche's tolcapone (Tasmar®) introduced in early 1998. These three new products are intended to be used early in the treatment of Parkinson's and may delay the need for levodopa therapy. Mirapex® with 2001 sales close to \$125 million and ReQuip® with sales of about \$60 million, offer benefits that might be considered to be only slightly superior to Parlodel® by Novartis and Permax® by Amarin, two products that have

been available in the marketplace for some time and are currently holding their own with 2001 sales in the \$55 million range.

Unlike Mirapex® and Requip®, COMT inhibitors, a new class of medications for the treatment of Parkinson's, represent what has been touted as a major advance and many patients who receive these medications experience rapid and clinically important improvement in their symptoms. They work in conjunction with levodopa by blocking one of the main enzymes (catechol-o-methyltransferase) responsible for the breakdown of levodopa in the bloodstream.

Tasmar® from Roche was the first of these agents to be launched. And, while it was initially well received and sold close to \$30 million in its first year, 1998, it has fallen off to less than \$7 million for 2001. In contrast, Novartis' entacapone (Comtan®), another COMT inhibitor, was launched in November 1999 and delivered nearly \$30 million in 2000 and nearly \$50 million for 2001. Right now it is too early to say how Comtan® will ultimately fare. We'll have to wait and see how sales for Comtan® develop in its next couple of years before we can say if this COMT inhibitor will significantly expand this market segment. At this point, it seems fairly clear that unless something changes with Tasmar®, it will not.

Other compounds being developed for use in Parkinson's disease include: Rilutek®, in Phase III from Aventis. (this product is already being used to treat ALS); PNU-95666, sumanirole, a dopamine-2 agonist from Pharmacia, and rotigotine CDS, a dopamine agonist from Schwarz Pharma, both also in Phase III; and TV-1203, a monoamine oxidase inhibitor in Phase III from Teva. Brasofensine from NeuroSearch, CPI-1189 from Centaur Pharmaceuticals; SPD-473 from Shire; spheramine from Titan/Schering AG; and NIL-A from Guilford Pharmaceuticals are all currently in Phase II for the treatment of Parkinson disease. ReQuip®, ropinirole, already marketed by GSK for Parkinson disease is

currently in Phase II for an expansion of its indication in this population.

Selegiline, an MAO-B inhibitor already in the marketplace and now available in regular tablet formulation generically, is also being developed in a rapidly dissolving tablet formulation under the brand name Zelepar® by Amarin. The submission for this formulation is currently being prepared for filing with FDA. This drug delivery technology could be especially beneficial in Parkinson’s disease patients because they often have difficulty swallowing, symptomatic of the illness. A transdermal patch formulation of selegiline, under the brand name Emsam®, is also being developed by Somerset Pharmaceuticals to treat depression, Alzheimer’s disease, and for neuroprotection in Parkinson’s disease. An irreversible MAO-B inhibitor in Phase III development for Parkinson’s is rasagiline, by Teva. Another product, Dostinex® (cabergoline) from Pharmacia was marketed in early 1997 and has shown strong growth delivering about \$40 million in 2000 and more than \$50 million in 2001. Its indication is for treatment of hyperprolactinemic disorders, but it is sometimes used in Parkinson’s much the way that Parlodel® was and is used.

If even a few of these improved new products and improved formulations reach the marketplace, as patients try and continue with these newer more expensive agents, there should be a more significant expansion of this market segment in the next five years compared to the general stagnation that we have seen previously.

One of the general non-drug approaches to treatment of CNS diseases including Parkinson’s involves the use of cellular material instead of drugs to supply the chemical substances required for normal function of brain cells. In Parkinson’s disease the neurons that make dopamine start to degenerate, damaging other brain cells and producing progressive loss of function. One treatment is to supply the missing dopamine

with drugs, but it appears that drugs eventually fail because too many neurons that process dopamine are lost as the disease progresses.

There have been attempts to use embryonic brain cells that can grow to replace the damaged neurons and the other brain cells harmed by lack of dopamine. Researchers consider fetal cells ideal for transplantation because of their ability to adapt and survive. Because they have not adopted the immunities normally acquired after birth, they are less vulnerable to rejection. There have now been scores of Parkinson’s patients around the world who have been injected with fetal cells, and some positive results have been observed. But, no patient has had full recovery and many unknowns remain such as how long the implanted cells will survive or if they will be rejected. There are also experiments underway in animals to use genetically engineered cells to reverse some forms of memory loss and Parkinson-like behavior. Analysts speculate that such research could lead to improved treatments for not only Parkinson’s, but also Alzheimer’s disease, epilepsy, diabetes and leukemia.

Another non-drug treatment for Parkinson’s disease is through implantation of a medical device called Activa® made by Medtronic. This device has been approved for some time for use on one side of the brain to control tremors on one side of the body. It is estimated that there are about 100,000 patients in the advanced stages of Parkinson disease who would benefit if they could have these devices implanted on both sides of their bodies to stimulate both sides of their brains and thus control tremors overall. Regulatory approval for such dual implantations is anticipated in the first half of 2002.

Awareness of Parkinson’s disease is continues to grow as our population ages and as personalities such as Michael J. Fox bring the illness into focus. There is some more data indicating that the incidence of Parkinson’s disease may be declining. New diagnostic tools that will allow for earlier

diagnosing of Parkinson's are being developed. One such methodology is Dopascan®, currently in Phase II from Guilford Pharmaceuticals.

Understanding of the etiology of Parkinson's may also be advancing through recent efforts in genetic research. There have now been reports of a common gene isolated among numerous members of a single family who have evidence of Parkinson's. Most recently a study has been released that suggests that caffeine consumption may have a neuroprotective effect against Parkinson's disease. If that data can be duplicated and/or supported, those who are not precluded from taking in caffeine for medical reasons may determine that caffeine is a worthwhile addition to their diet for reasons beyond the 'morning jump-start'.

Stroke

In the preventative treatment of stroke, Roche's Ticlid® (ticlopidine) sales grew to about \$230 million in 1998 prior to the marketing of generics. Since the advent of ticlopidine generics, Ticlid® sales have dropped, off more than 90% for 2001 versus 1998. Several companies are working to develop products for the chronic treatment of patients with prior stroke or risk factors for stroke. Some of these products are also likely to be beneficial for patients who have suffered head trauma. One product similar to Ticlid® but reported to have a better profile relative to serious hematological effects is Bristol-Myers Squibb's Plavix® (clopidogrel). It is a once-a-day, orally active platelet aggregation inhibitor, licensed from Sanofi. During 1998, its first year on the U.S. market, it sold nearly \$120 million and grew to more than \$1.1 billion in 2001. Worldwide sales of Plavix® in 2001 were nearly \$2 billion and all indications are that this preventative treatment market may continue to grow at double-digit rates for some time.

Specifically for prevention of stroke, Boehringer Ingelheim has combined its

extended-release dipyridamole along with aspirin in a capsule formulation as Aggrenox®. The indication is to reduce the combined risk of death and nonfatal stroke in patients who have already experienced a transient ischemic attack (a mini-stroke) or previous ischemic stroke. Approval was received late in November 1999 and the product was launched the following month. Sales of nearly \$25 million in 2000 and nearly \$70 million in 2001 suggest that U.S. physicians believe this product is a better alternative compared to aspirin alone or the two products taken individually. Boehringer Ingelheim is betting that the simplicity of dosing will make Aggrenox® a major player in this market.

Other products are also late in development for the prevention or treatment of stroke. Bristol-Myers Squibb (BMS) has a potassium channel opener entry known only as MaxiPost® or Maxi-K® in Phase III for treatment of acute ischemic stroke. BMS has touted Maxi-K® to be a 'blockbuster' drug that will sell a billion or more following launch, possibly as early as 2003. Repinotan, a 5HT_{1A} agonist from Bayer Corp. is also in Phase III for treatment of acute ischemic stroke.

Several other compounds are in Phase II development for stroke including three from GSK, SB424323, an indirect thrombin inhibitor for prevention of stroke; S-0139, an endothelin A receptor antagonist for treatment of ischemic and hemorrhagic stroke, and sipatrigine, a sodium channel inhibitor. Others in Phase II are CJ-15161, a Kappa agonist for treatment of stroke and UK279,276 for treatment of reperfusion injury associated with acute ischemic stroke, both from Pfizer; Cerebril® from Neurochem for hemorrhagic stroke; BAY x 3702, a cholinesterase inhibitor for acute treatment of stroke from Bayer; and NXY-059, a radical scavenger for treatment of stroke from AstraZeneca; Several biotech companies are working in collaboration with major pharmaceutical companies on products in

earlier stages of development for the prevention and/or treatment of stroke and there is some suggestion that all NSAIDs in small daily doses provide a certain degree of protection from future stroke. Similarly, clinical data being collected suggests that ongoing treatment with some of the cholesterol reducers such as Zocor® and Lipitor® provide a similar protection.

Attention Deficit Hyperactivity Disorder

The U.S. market for the treatment of children and adults with attention deficit hyperactivity disorder (ADHD) has grown over the past few years and for 2001 it now exceeds \$1.1. The first major new product to enter this market was Shire's Adderall®, a combination of dextroamphetamine and amphetamine. This product grew from less than \$10 million in 1996 to more than \$350 million in 2001 predominantly based on the claim that the dextroamphetamine acted and dissipated quickly while the amphetamine portion of the product acted less quickly and had a more lasting effect. It is labeled for dosing the same as other dextroamphetamine products. In late 2001 Shire marketed Adderall® XR, a longer acting version of Adderall®, in an effort to provide a longer-acting dextroamphetamine product that would compete with the large number of newer long-acting methylphenidate products that have recently been launched (see below). Shire anticipates that the Adderall® XR product will become its number one brand by 2002.

Despite negative press related to overuse of these products and over-treatment of ADHD, prescriptions have continued to grow by about 10% each year. As the market was expanding with increased treatment of ADHD overall, other product formulations were also being developed with the goal of delivering the daily medication with a reduced frequency of dosing and with special emphasis on eliminating the need for a mid-day (school lunch-time) dose.

Four such methylphenidate products have now reached the marketplace. Metadate® ER was launched by Celltech at the end of 1999 and delivered about \$10 million in its first year; Metadate® CD was launched by Celltech in mid-2001 with first year sales of about \$8 million; Methylin® ER from Mallinckrodt was launched in mid-year 2000 and also sold about \$8 million during 2001. The last product, Concerta® from Alza with co-marketing by McNeil, was introduced in August 2000; delivered year 2000 sales of over \$60 million in just 5 months and nearly \$350 million in 2001, its first full year on the market. At the rate it is going, it will overtake the market leading Adderall® line by the end of 2002, its second full year on the market. The Concerta® formulation provides a truly once-a-day dosing regimen for most patients. Concerta® is also in Phase III for cancer treatment-related fatigue. A somewhat different methylphenidate formulation is Noven Pharmaceuticals' MethyPatch®, a transdermal methylphenidate system that will provide medication through application of a daily patch. This formulation has now completed Phase III and is being prepared for submission to FDA. Approval is anticipated in 2003.

Not to be outdone, the Ritalin® innovator, Novartis, has two additional formulations of their product under review. The first, Focalin™, is a “short-acting, for flexible dosing” version of the active isomer of methylphenidate known as dexmethylphenidate. The second is a ‘truly once-a-day, twelve hour’ version trademarked as Ritalin® LA™. Both of these new products should be marketed in 2002 and it will be interesting to see how the market shakes out as it continues to grow over the next couple of years.

In the meantime, other products are in development for this disorder for treatment of both children and adults. Strattera®, atomoxetine, a norepinephrine reuptake inhibitor from Lilly, for ADHD treatment in children aged 7 to 13, adolescents and adults is currently being reviewed at FDA. Unlike

the amphetamine and methylphenidate products, this agent would not be a controlled substance and would therefore be more likely to be prescribed and used without concern about abuse. If this product is shown to be equally as safe and effective as the current brands, but without the potential for abuse perceived with these current alternatives, more of the families who have been counseled to have their youngsters treated for ADHD may choose a trial of medication instead of refusing for fear of abuse and/or addiction.

Another product in Phase III development for ADHD in children 7 to 18 years of age is mecamlamine (Inversine®), a nicotinic antagonist from Layton BioScience. Two products in Phase II for ADHD are Aricept®, donepezil, for treatment of children 7 to 16 years of age, from Eisai; and a noradrenaline reuptake inhibitor known only as GW320659 from GlaxoSmithKline. Altoprane, a radioimaging agent intended to aid in the diagnosis of attention deficit hyperactivity disorder from Boston Life Sciences is also currently in Phase II.

As these new formulations and treatments for ADHD make their way into the marketplace over the next year or two, we can expect to see further growth of both prescriptions and dollars in this market segment. It is likely that a successful launch of Strattera® by Lilly in the first half of 2003 will have the major impact on the treatment of ADHD in the U. S. since it will represent the only really new entity to enter this treatment arena in several decades.

Multiple Sclerosis (MS)

In another of what used to be one of the smaller markets, the treatment of multiple sclerosis (MS), an interferon based drug, Avonex®, from Biogen was introduced in May, 1996 and garnered close to \$400 million in U.S. sales for 2001 (nearly \$1 billion worldwide). Betaseron®, marketed by Berlex/Schering AG with 2001 sales of about \$100 million in the U. S. (over \$600 million

worldwide) was the initial interferon product in this market when it was introduced in 1993, but it was quickly overtaken by Avonex®, once the latter was introduced. Both products are looking to expand their indications. Betaseron® is currently awaiting approval for treatment of secondary-progressive MS to slow progression of the disease and reduce the frequency of relapses. Avonex® is currently awaiting approval for treatment of patients who are at high risk of developing clinically definite multiple sclerosis, or after a patient has one multiple sclerosis attack and when alternative diagnoses have been excluded. Avonex® is also in Phase III clinicals to treat brain atrophy in patients suffering from relapsing-remitting multiple sclerosis. Since Avonex® is generally administered by a healthcare professional, it is somewhat less convenient for the patient, but it may be cost effective for some patients because injectables that are not self-administered can qualify for Medicare coverage.

A product awaiting FDA approval to delay the progression of relapsing-remitting multiple sclerosis and to treat secondary progressive multiple sclerosis is Rebif®, a recombinant interferon beta-1a from Serono. Non-U.S. sales for Rebif® in 2001 were nearly \$400 million, but unless Rebif® outperforms Avonex® in a head-to-head study, the Rebif® U. S. approval may be blocked until 2003 by orphan exclusivity for Biogen's Avonex®. Pending the results from this head-to-head study of Rebif® versus Avonex®, FDA will decide whether or not to allow marketing of Rebif® prior to the end of Biogen's exclusivity period. Early data from the study suggest that the results will show Rebif® to have an efficacy advantage over Avonex®. If this trend holds, Rebif® could be approved for marketing as early as 1st quarter 2002. If it has an efficacy advantage, it is estimated that Rebif® will be priced at a premium of 25-35% versus Avonex® at introduction - perhaps as much as \$1300 for a month's therapy.

Another Phase III study for Rebif® is underway for the early treatment of multiple sclerosis.

Cladribine, a product that is already on the market in injectable form for the treatment of hairy cell leukemia, is also in Phase III development by Ivax for use in the treatment of chronic, progressive, non-remitting multiple sclerosis. Another monoclonal antibody compound aimed at reducing the severity and duration of an MS attack is Antegren®, natalizumab, from Biogen, now in Phase III.

A non-interferon based injectable product, Copaxone®, glatiramer acetate from Teva, received FDA approval in December, 1996 for reducing relapse in multiple sclerosis patients and launched in March, 1997 delivering sales of just over \$10 million for the year. It's high price of \$7,000 to \$10,000 per patient, per year may have initially limited uptake, however sales for 2001 have continued to strengthen to about \$300 million suggesting that it is providing some significant benefit in relapse reduction and stopping progression of disability for patients. A separate Phase III effort is underway in support of an oral formulation of Copaxone® for treatment of relapsing-remitting MS. This should further expand its use.

Other agents in development for MS include: NBI-5788 from Neurocrine Biosciences in Phase III; AnergiX, a human leukocyte antigen in Phase II for MS from Corixa Corp.; BMS 188667, an immunomodulator from Bristol Myers Squibb in Phase II; a cytokine antagonist from Schering AG in Phase II; Fampridine-SR, a potassium channel blocker intended to restore neurological function in MS from Elan in Phase II; J695, a human monoclonal antibody, IL-12 inhibitor from Wyeth in Phase II; NeuroVax, a receptor peptide from Immune Response Corp. in Phase II; and teriflunomide from Aventis in Phase II. Cephalon's Provigil® is also in Phase II for treatment of the fatigue associated with MS.

Other

A previously marketed pharmaceutical agent has also been developed as a smoking cessation aid. A sustained-release bupropion was marketed as Zyban® in mid-1997 and delivered nearly \$150 million in U.S. sales for the year 1998 and then dropped off to about \$100 million annually for the years from 1999 through 2001 (Zyban® is another name for Wellbutrin® SR, a GlaxoSmithKline antidepressant.) Pfizer also has CP 526,555, a nicotinic antagonist in Phase II development for smoking cessation.

In other segments based on dependency, Vivitrex®, naltrexone, is in Phase III development by Amylin Pharmaceuticals and Alkermes for the treatment of alcohol dependence, NeuroSearch AS has a compound known only as NS2359, a monoamine reuptake inhibitor in Phase II for the treatment of cocaine addiction, and Xenova Group Plc. has a cocaine protein conjugate known as TA-CD in Phase II for cocaine addiction.

In an even smaller market, Aventis introduced a first market entry, riluzole (Rilutek®), for the treatment of ALS (amyotrophic lateral sclerosis) in 1996. Despite a cost of nearly \$10 per tablet, U.S. sales were less than \$20 million in 1997, the product's first full year in the marketplace. They have now grown to nearly \$35 million in 2001. This market may expand if and when the Cephalon mecasermin product, Myotrophin®, currently filed and awaiting FDA review, becomes available for the treatment of ALS. A Phase III effort is underway in support of xaliproden, an antineurodegenerative agent from Sanofi-Synthelabo for treatment of ALS. This disease can be very difficult to treat and several products that had initially appeared beneficial have failed to differentiate from placebo during Phase III studies. The availability of orphan drug status will continue to foster research in this very limited market.

A product is being developed for treatment of another disease that warrants orphan drug status. That is LAX-101 from Amarin Corp. which is in Phase III for treatment of Huntington disease.

Participants

There are a number of established competitors in Central Nervous System Pharmaceuticals. The leaders in the U.S. market are tabulated below. Notable among the recent important arrivals are: Alza with Concerta® for ADHD; Biogen with Avonex®, interferon for treatment of multiple sclerosis; Teva with it’s Copaxone® treatment for MS; Organon (Akzo Nobel), with Remeron® for depression; Eisai Co., Ltd. with Aricept® an entry for the treatment of Alzheimer’s; Shire, with its Adderall® line for attention deficit disorder; and UCB

Pharma with Keppra, a new entry among the anticonvulsants. Aventis, a long established pharmaceutical presence, has entered the CNS market with Anzemet® for nausea and vomiting and Rilutek® for ALS. Similarly, Merck has come back to the CNS market after an absence of many years with Maxalt® and Maxalt® Melt for migraine and Sanofi-Synthelabo will be a major force as it takes back the compounds such as Ambien® and Plavix® that others have marketed.

In addition, there are a number of emerging companies focused on neuroscience including Amarin, Ancile Pharmaceuticals, Axonyx, Elan,, Centaur, Cephalon, Chiron, CoCensys, Cognetix, Cortex Pharmaceuticals, Guilford Pharmaceuticals, Neurochem, Neurocrine Biosciences, Neurogen, NeuroSearch AS, NPS Pharmaceutical, Schwarz Pharma, Xenova Group and Synaptic Pharmaceutical.

Participants (\$ millions)

U.S. Revenues	2000	2001
Abbott	1,030	1,270
AstraZeneca	560	920
Bristol-Myers Squibb	1,840	2,100
Forest Labs	720	1,160
Glaxo SmithKline	4,430	5,930
Johnson & Johnson	1,500	2,110
Lilly	4,150	4,780
Novartis	610	820
Pfizer	3,120	4,400
Pharmacia	910	1,260
Wyeth	1,080	1,550

Sources: Dorland Biomedical Database, industry sources; commentary provided by: M. Lynn Childs, Principal, Valley Forge Marketing Consultants