The Pharmacist Activist

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Editorial

When Price Controls are Established for Drugs,

Big Pharma will have Only Itself to Blame

I have been opposed to the establishment of price controls for drugs, even though I have had concerns about the pricing/marketing "strategies" some pharmaceutical companies have employed. However, I am quickly approaching the point where I will be an advocate for such price controls because of what I consider to be grossly excessive prices for a growing number of medications. Some of the new anticancer medications provide blatant examples.

Lenalidomide (Revlimid-Celgene), sorafenib (Nexavar-Bayer; Onyx), and sunitinib (Sutent-Pfizer) are important new medications for types of cancer for which treatment options are very limited. I commend the research that resulted in their development and their approval by the Food and Drug Administration. That research is expensive, the patient populations in whom the drugs will be used are small, and the drugs will not be used for extended periods of time. Pharmaceutical companies need to make a profit to fund the research that will result in the development of even better drugs. But how much profit is appropriate?

The cost of each of these three medications is more than $5,000 a month! These medications are administered orally as capsules or tablets. They are not cures for the cancers they are approved to treat, but may prolong survival. They are often used in combination with other expensive anticancer drugs. The specific costs for a 30-day supply (based on the recommended dosages) of these medications is noted below (based on information in the July 15, 2006 issue of *Price Alert* [Medi-Span, Wolters Kluwer Health]).

Nexavar tablets 200 mg	**$5,416.25**
Revlimid capsules 10 mg	**$8,437.50**
Sutent capsules 50 mg*	**$8,015.63**

**Sutent is used in a dosage regimen of 4 weeks on treatment followed by 2 weeks off treatment.*

Some will respond to this situation by noting that Medicare, Medicaid and other insurance programs will cover much of the cost of these medications, and that pharmaceutical companies have programs that will help patients with financial challenges obtain needed medications. However, many individual patients still will not have adequate financial resources to afford these and other expensive medications and, with increasing frequency, questions are being asked regarding the extent to which society/government should be expected to assume much of the cost for such expensive therapies.

Many cancers are life-threatening with the result that many of these patients and their families are under great stress in dealing with the treatment of the disease, as well as the serious personal and financial implications. They should not have an added burden of coping with the stunningly high prices (more than $200 a capsule) for some of their medications. They should not be forced to make critical decisions regarding their treatment based on the costs that will be incurred. However, an increasing number of patients are faced with these types of questions/decisions: Is the possible additional one month (or 3 months, or 6 months) of life worth the cost that I and my family will incur? Even some of those who may be in a financial position to afford the medications will decide to forego treatment because they do not want to risk exhausting their savings and/or do not wish to compromise the financial security of their family members.

It is inevitable that some life-threatening illnesses/experiences are associated with serious financial challenges. However, the difference in the situation addressed here is the perception that an already highly profitable industry is charging exorbitant prices for its medications to people who are in the weakest position to respond. There is increasing recognition of this situation and

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News, Information and Career Opportunities
NEWS - Line PUBLISHING

(Blame cont.)

an unwillingness to continue to tolerate it as reflected by recent stories in the lay press such as, "Cost of cancer drugs crushes all but hope" (*USA Today*, July 11, 2006), "Prices Soar for Cancer Drugs" (*USA Today*, July 11, 2006), and "Wary of backlash, cancer-drug makers weigh price limits" (*Wall Street Journal*, May 10, 2006).

In addition to medications to treat cancers, there are numerous other drugs for which there are concerns about the prices that the pharmaceutical companies charge. These have been the concerns that have fueled ongoing debates on topics such as importing medications from Canada. Although public outrage regarding the prices of medications was overshadowed by the outrage at the price of gasoline and the oil industry, some pharmaceutical companies seem almost determined to reclaim a share of the outrage spotlight by the prices they are charging for anticancer drugs. And some observers are concerned that if companies are allowed to get away with the prices they are charging patients with an illness as devastating as cancer, what will stop them from also charging even higher prices for other medications than they are now?

The answer to that question is that, at the present time, companies can charge whatever they want to for medications. However, we are rapidly approaching the time when individual patients and the general public will no longer be willing to accept the high costs associated with drug therapy.

Price controls are the greatest fear of the pharmaceutical companies. However, if they do not exercise greater restraint in their pricing of medications than they have demonstrated to date, price controls will be established. And these companies will have only themselves to blame.

Daniel A. Hussar

A Positive Step

The National Association of Chain Drug Stores (NACDS) and the National Community Pharmacists Association (NCPA) have announced the formation of the Coalition for Community Pharmacy Action (CCPA). This initiative is a very important and positive step that will permit the parent organizations to more effectively promote the services provided by community pharmacists, both chain and independent, and respond to the legislative, financial and other influences that threaten community pharmacists, as well as the scope and quality of the services they provide to the members of their communities.

There will continue to be issues on which independent pharmacists and chain pharmacies have different positions and these must also be addressed. However, the establishment of CCPA demonstrates the recognition of NACDS and NCPA that there are extremely important challenges that can be most effectively addressed in a united manner.

This action is important not only for community pharmacists, but for the entire profession. The reputation of and respect for our profession are more dependent upon the relationship between the public and local pharmacists than any other factor. Pharmacists in other areas of responsibility (e.g., hospitals, colleges of pharmacy, pharmaceutical companies) should seek out opportunities to support our colleagues in community pharmacy practice and this initiative in their behalf. Our profession and the patients served will benefit as a result.

Daniel A. Hussar

New Drug Review

Rasagiline mesylate (Azilect)

New Drug Comparison Rating (NDCR) = 3

(no or minor advantage(s)/ disadvantage(s), or advantage(s) and disadvantage(s) of similar importance)

in a scale of 1 to 5, with 5 being the highest rating

Indications:

For the treatment of the signs and symptoms of idiopathic Parkinson's disease as initial monotherapy and as adjunct therapy to levodopa.

Comparative drugs:

Selegiline (e.g., Eldepryl, Zelapar)

Advantages:

- Labeled indications include initial monotherapy for Parkinson's disease.
- Is administered once a day (compared with Eldepryl and generic formulations that are administered twice a day; however, Zelapar is administered once a day).
- Is not converted to amphetamine metabolites.

Disadvantages:

- Consumption of tyramine-rich foods, beverages, and dietary supplements should be restricted.
- Labeling is more restrictive with respect to the potential for interactions with other drugs (e.g., concurrent use with a larger number of drugs is contraindicated).
- Interacts with CYP1A2 inhibitors (e.g., ciprofloxacin, fluvoxamine)—action of rasagiline may be increased.
- More expensive (compared with Eldepryl and generic formulations).

Conclusions:

Rasagiline is a selective inhibitor of monoamine oxidase type B (MAO-B) with properties that are most similar to those of selegiline. Both agents are indicated as adjunct therapy to levodopa, and rasagiline is also indicated as initial monotherapy. However, neither agent is likely to be used often as initial therapy for Parkinson's disease. Rasagiline has not been directly compared with selegiline in clinical studies.

Rasagiline and selegiline probably have a similar risk for adverse events and drug interactions related to their MAO inhibitory activity when they are used in the recommended dosages. However, a dosage has been identified for selegiline that is not likely to be associated with a risk of interactions with tyramine-containing dietary items, but such a dosage has not yet been established for rasagiline. Accordingly, there are prominent warnings in the labeling for rasagiline, but not selegiline, about the need to restrict dietary tyramine. In addition, the labeling for rasagiline identifies a larger number of drugs with which concurrent use is contraindicated (e.g., cyclobenzaprine, mirtazapine, St. John's wort, sympathomimetic amines) than are included in the labeling for selegiline formulations. Rasagiline is a substrate for CYP1A2, and its action may be significantly increased by the concurrent use of drugs that inhibit this metabolic pathway (e.g., ciprofloxacin, fluvoxamine).

Selegiline is converted, in part, to amphetamine metabolites, whereas rasagiline is not. This may be considered an advantage for rasagiline, but it is not known whether this difference is associated with a lower incidence of drug-related problems.

Selegiline, as Eldepryl and generic formulations, is administered twice a day. Rasagiline is administered once a day which is an advantage over these products; however, an orally-disintegrating tablet formulation of selegiline (Zelapar) has been recently approved for once-daily administration, and in a lower dosage than with the other formulations of selegiline. Therefore, both agents are available in formulations that are administered once a day. Whether these agents are administered once or twice a day is not as important a difference as it may be with some other therapeutic agents because rasagiline and selegiline are usually administered in a regimen that includes levodopa that must be administered more than once a day.

Rasagiline is considerably more expensive than Eldepryl or the generic formulations of selegiline, but is slightly less expensive than Zelapar when the latter is used in a dosage of 2.5 mg once a day.

There is no evidence to indicate that rasagiline is more effective or safer to use than selegiline. Indeed, there may be a greater risk of interactions between rasagiline with certain other medications and dietary items. The once daily administration of rasagiline is matched by the new formulation of selegiline (Zelapar). Selegiline should be the drug of choice from among these two agents and, unless twice daily administration is not feasible, can be used at a much lower cost.

Discussion

Rasagiline mesylate (Azilect-Teva) is an irreversible monoamine oxidase (MAO) inhibitor that is thought to selectively inhibit MAO type B (MAO-B), the major form of MAO in the human brain. Its properties and use are most similar to those of selegiline (e.g., Eldepryl, Zelapar), and their inhibition of MAO-B results in increased dopamine concentrations in the striatum, although other mechanisms of action may also contribute to their ability to reduce the symptoms of Parkinson's disease.

Rasagiline is indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease as initial monotherapy and as adjunct therapy to levodopa. The labeled indication for selegiline is as an adjunct to levodopa/carbidopa, and does not include initial monotherapy. However, neither agent is likely to be used often as initial therapy for Parkinson's disease.

The effectiveness of rasagiline was demonstrated in three placebo controlled studies. In two of these studies, rasagiline was used as adjunct therapy to levodopa and reduced the total daily "off" time (i.e., period of relatively poor function and mobility). The baseline daily "off" time for patients in these studies was approximately six hours. The patients treated with rasagiline (1 mg daily) had an average reduction in "off" time of 1.9 hours and 1.2 hours in the two studies, compared with 0.9 hours and 0.4 hours, respectively, in those receiving placebo. Rasagiline and selegiline have not been directly compared in clinical studies.

The adverse events reported most frequently when rasagiline was used as monotherapy include arthralgia (7%), dyspepsia (7%), depression (5%), flu syndrome (5%), and fall (5%). When used as an adjunct to levodopa, rasagiline may increase dopaminergic adverse events and exacerbate pre-existing dyskinesia (18% incidence in those receiving rasagiline compared with 10% in those receiving placebo). The potential for postural hypotension (9%) is also greater in those treated with both rasagiline and levodopa.

Epidemiological studies have shown that patients with Parkinson's disease have a higher risk (2- to 4-fold higher) of developing melanoma than the general population, although it has not been determined whether the increased risk is related to the disorder or the drugs used to treat it. In the studies with rasagiline, the risk of melanoma was higher in patients treated with the drug than in the general population and patients should be monitored for this possibility on a frequent basis.

Drugs that inhibit MAO are associated with a high risk of interactions with certain medications and dietary items. The inhibition of MAO-A is more likely to result in serious and even life-threatening interactions than the inhibition of MAO-B. MAO-A is the primary form of MAO in the gastrointestinal tract and liver and provides protection against the pressor effects of exogenous amines such as tyramine. Selegiline is thought to selectively inhibit MAO-B if the dosage of the conventional tablet and capsule formulations (Eldepryl and generic formulations) does not exceed 10 mg per day and if the dosage of the new orally-disintegrating tablet formulation (Zelapar) does not exceed 2.5 mg per day. Although rasagiline may also selectively inhibit MAO-B, a specific dosage below which it only inhibits MAO-B (and not MAO-A) has not been identified and its labeling contains contraindications and warnings regarding interactions with a larger number of drugs and dietary items than does the labeling for the selegiline formulations.

The use of rasagiline is contraindicated in patients treated with another MAO inhibitor (e.g., selegiline, tranylcypromine [e.g., Parnate]), or a sympathomimetic amine (e.g., amphetamines, phenylephrine, pseudoephedrine) because of the risk of severe hypertensive reactions. Concurrent use with meperidine (e.g., Demerol) is also contraindicated because of a risk of severe reactions, as is concurrent use with methadone, propoxyphene (e.g., Darvon), or tramadol (e.g., Ultram). Because of reports of psychosis or bizarre behavior associated with the concurrent use of other MAO inhibitors and dextromethorphan, the concomitant use of rasagiline with this agent, as well as with cyclobenzaprine (e.g., Flexeril), mirtazapine (Remeron), or St. John's wort, is contraindicated.

The labeling for rasagiline also includes warnings regarding concurrent use of the new drug with a tricyclic antidepressant (e.g., amitriptyline), selective serotonin reuptake inhibitor (SSRI; e.g., fluoxetine [e.g., Prozac]), or serotonin-norepinephrine reuptake inhibitor (SNRI; e.g., venlafaxine [Effexor]) because of reports of serious interactions (e.g., hyperthermia, autonomic instability, agitation, delirium) of other MAO inhibitors with these agents.

Patients treated with an MAO-A inhibitor are known to be at risk of serious adverse events (e.g., severe headache, visual disturbances, hypertensive crisis) if they consume tyramine-rich foods (e.g., aged cheeses, aged and fermented meats), beverages (e.g., red wines), or dietary supplements. The selectivity of rasagiline for inhibiting MAO-B (and not MAO-A) in humans has not been sufficiently characterized to permit its use without restriction of dietary tyramine. Patients to be treated with rasagiline should be instructed regarding the tyramine content of foods and beverages and the need to restrict certain dietary items.

Rasagiline is extensively metabolized in the liver, primarily via CYP1A2 pathways. Unlike selegiline, it is not converted to amphetamine metabolites, but it is not known whether this difference is associated with a lower incidence of drug-related problems. The concentration and activity of rasagiline may be significantly increased by the concurrent use of a CYP1A2 inhibitor (e.g., ciprofloxacin [e.g., Cipro], fluvoxamine), and therapy should be closely monitored.

Rasagiline is administered once a day without regard to food. The Eldepryl and generic formulations of selegiline are administered twice a day, but the new orally-disintegrating tablet formulation of selegiline (Zelapar) is administered just once a day. When used as monotherapy, the recommended dosage of rasagiline is 1 mg once a day. When used as an adjunct to levodopa, the recommended initial dosage is 0.5 mg once a day; if a satisfactory clinical response is not attained, the dosage may be increased to 1 mg once a day. A dosage of 0.5 mg once a day is recommended in patients with mild hepatic impairment or patients who are being treated concurrently with a CYP1A2 inhibitor.

Rasagiline mesylate is supplied in tablets in quantities that provide 0.5 mg and 1 mg of rasagiline base.

Daniel A. Hussar and Ezra P. Mell

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