The Pharmacist Activist

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Editorial

Daraprim – The Ultimate Drug Pricing Outrage?

Pyrimethamine (Daraprim) was initially approved in the United States in 1953 for the treatment of patients with malaria. It was subsequently determined to be of value in the treatment of toxoplasmosis, a relatively uncommon but sometimes fatal parasitic infection for which patients with compromised immune systems (e.g., patients with AIDS) are at greatest risk. Pyrimethamine is a component of the regimen that has been considered to be the most effective treatment for toxoplasmosis.

Pyrimethamine was originally developed and marketed by the Burroughs Wellcome Company (subsequently acquired by the company now known as GlaxoSmithKline). Following expiration of its patent, the product and its trade name Daraprim have been acquired and marketed by several other companies. Generic formulations of the drug have either been unavailable or available on only a limited basis because the drug is used so infrequently that generic companies have not considered it commercially feasible to market. As recently as 5 years ago, the cost of Daraprim was about $1 a tablet. The US marketing rights to the drug in the United States were sold by GlaxoSmithKline in 2010, and the rights to the drug have been sold several additional times during the last five years. In the period preceding August, 2015 Daraprim was marketed by Impax Laboratories at a cost of $13.50 a tablet.

Turing Pharmaceuticals

In August, 2015 Impax sold Daraprim to Turing Pharmaceuticals. Shortly prior to that time Impax discontinued distributing the drug through the traditional pharmacy system and restricted its availability to a controlled distribution system, resulting in only very limited supplies of the drug remaining available in general distribution.

The CEO of Turing is a former hedge fund manager and a former CEO of a small pharmaceutical company (Retrophin), another company that acquired an older infrequently prescribed drug (tiopronin [Thiola] for the prevention of cystine kidney stones) that was not available from other sources, and then markedly increased its price.

Following its purchase of Daraprim in what has been described in commentaries as an "overnight" price increase, Turing raised the price of Daraprim from $13.50 a tablet to $750 a tablet. The company and its CEO initially attempted

to justify the price increase by describing it as a great business decision that would be of benefit for all of its stakeholders. The previous price was identified as unprofitable and the drug was portrayed as being so infrequently prescribed that the impact of the price increase would be minuscule. The Turing CEO was quoted as saying, "This isn't the greedy drug company trying to gouge patients, it is us trying to stay in business" (*New York Times*, September 20).

Outrage!

Daraprim is not the first drug for which the availability of an older drug has been limited/restricted/controlled with a resultant sharp increase in its price. Examples include tiopronin, doxycycline, cycloserine, isoproterenol, repository corticotropin injection (H.P. Acthar Gel), and hydroxyprogesterone caproate (Makena). However, the outrage regarding the Daraprim price increase from patients, health professionals, legislators, Presidential candidates, and the public has been immediate and intense. This response is certainly due, in large part, to the huge amount of the price increase, profit being the single motivation for the increase, and the arrogance of the company and its CEO in attempting to justify the increase. This situation has also occurred during a time period in which numerous concerns have been voiced about the prices of many drugs, including important drugs for chronic hepatitis C infection, cholesterol-regulating drugs with a unique mechanism of action, and many anticancer drugs. The Daraprim experience has become a "lightning rod" that has galvanized attention to all examples and reasons for which many have concerns about drug prices. It has to be the worst nightmare for the Pharmaceutical Research and Manufacturers of America (PhRMA) and the Biotechnology Industry Organization (BIO) that represent the interests of the pharmaceutical companies, and are very concerned that their member companies' motives and actions might be considered to be similar to those demonstrated by Turing. BIO issued the following statement in response to the Daraprim situation:

> "Turing Pharmaceuticals was a member of BIO for a brief period of time and is currently no longer a member. The company and its leadership do not reflect the commitment to innovation and values that are at the core of BIO's reputation and mission. For that reason, BIO determined, after a review of Turing's membership status, that the company did not meet our eligibility criteria, and we took action to rescind its membership and return its membership dues."

I commend BIO for taking this action. However, an evaluation of "the commitment to innovation and values" of certain other companies is also warranted. Although the price increase and statements from Turing may be the most blatant and arrogant to date, some other companies are also engaged in similar practices that are motivated only by the anticipation of large profits.

The storm of criticism and anger regarding the price increase for Daraprim resulted in an announcement from Turing several days later that it would lower the price although, at the time this is being written, the reduced price had not yet been identified. Turing also attempted to convey a message that the higher price was needed to fund research regarding toxoplasmosis and the development of educational programs and new drugs from which patients would benefit. It also indicated that the medication would be provided to patients with financial need. However, its singular motivation for high profits had already been exposed, and its belated attempt to claim it was interested in patients only further eroded its credibility.

A better outcome

The antitubercular drug cycloserine was developed in the 1950s but is seldom used in current therapy. However, it is of value in the treatment of patients with potentially life-threatening multi-drug resistant tuberculosis that is resistant to conventional antitubercular regimens. Cycloserine capsules have been supplied by The Chao Center, a nonprofit organization that is part of the Purdue Research Foundation, at a cost of $480 for 30 capsules. It recently sold the product to Rodelis Therapeutics. When it was learned that Rodelis planned to increase the price of cycloserine to $10,800 for 30 capsules, Chao requested that the rights to the drug be returned. The two companies agreed that the sale of the drug

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New Drug Review

Suvorexant
(Belsomra – Merck)

Hypnotic

New Drug Comparison Rating (NDCR) = 4
(significant advantages)
in a scale of 1 to 5 with 5 being the highest rating

Indication:
Treatment of patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance.

Comparable drugs:
Zolpidem extended-release (e.g., Ambien CR), eszopiclone (Lunesta).

Advantages:
- Has a unique mechanism of action (orexin receptor antagonist);
- May be less likely to cause withdrawal effects when treatment is discontinued.

Disadvantages:
- Has not been directly compared with comparable drugs in clinical studies;
- Is more likely to cause cataplexy-like symptoms and is contraindicated in patients with narcolepsy.

Most important risks/adverse events:
Risk of excessive central nervous system (CNS) actions (e.g., impaired daytime wakefulness and alertness, impaired driving; risk is increased by the concurrent use of other CNS depressants including alcohol; all patients should be cautioned regarding the CNS effects and related risks; patients treated with a dosage of 20 mg daily should be advised against next-day driving and other activities requiring complete mental alertness); nighttime "sleep-driving" and other complex behaviors while out of bed and not fully awake, with amnesia for the event; cataplexy-like symptoms (is contraindicated in patients with narcolepsy); worsening of depression or suicidal thinking; risk of abuse (is classified as a Schedule IV controlled substance); additive CNS effects result when used concurrently with other CNS depressants (consumption of alcoholic beverages is best avoided, particularly at bedtime and in the evening); action may be increased by CYP3A inhibitors (concurrent use with a strong CYP3A inhibitor [e.g., clarithromycin, itraconazole] is not recommended; dosage should be reduced in patients also taking a moderate CYP3A inhibitor [diltiazem, verapamil, grapefruit juice]); action may be reduced by the concurrent use of a strong CYP3A inducer (e.g., carbamazepine, St. John's wort); may increase digoxin concentrations.

Most common adverse events:
Somnolence (7%).

Usual dosage:
10 mg once a night within 30 minutes of going to bed, with at least 7 hours remaining before the planned time of awakening; onset of action may be delayed if taken with or soon after a meal; if the 10 mg dose is well tolerated but not effective, the dose can be increased; the maximum recommended dosage is 20 mg once daily; if it is necessary for a patient to also be taking a moderate CYP3A inhibitor, the recommended initial dosage is 5 mg once a night, and the dosage should generally not exceed 10 mg daily in these patients; a reduction in dosage may be necessary in patients taking other CNS depressants, and in obese female patients.

Products:
Film-coated tablets – 5 mg, 10 mg, 15 mg, 20 mg.

Comments:
The orexins are naturally occurring neuropeptides that act in a signaling system as a central promoter of wakefulness. This wake-promoting action results, at least in part, from

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would be canceled and the rights to the drug were returned to Chao. Although Chao considers it necessary to raise the price to approximately $1,050 for 30 capsules, this is only about one-tenth of the price Rodelis had planned to charge.

Other options

The Daraprim experience represents an abuse of the drug distribution system and undermining of its already fragile financial viability. These situations must not be tolerated. One strategy is to have the company that initially obtained approval for the drug or a generic pharmaceutical company supply the drug at a low profit margin. The situation described above in which cycloserine is supplied by a nonprofit organization is a variation of this approach.

Another option is to have compounding pharmacists obtain the medication and prepare the appropriate dosage forms. Although there are restrictions with respect to pharmacists compounding formulations that are commercially available, this situation needs to be reconsidered and exceptions to the restrictions explored.

Another option is to obtain certain medications from a Canadian pharmacy. I have not been an advocate for US residents obtaining medications from Canada and other countries. However, it is my understanding that pyrimethamine tablets cost between $6 and $7 each from a Canadian pharmacy, compared to $750 that Turing was planning to charge in the US. This difference can't be justified and current restrictions must be reconsidered.

The concerns about the prices for new drugs and other drugs that still have patent protection are complex and beyond the scope of this commentary. However, for older drugs for which the patents have expired, the options identified above should be actively pursued to prevent greedy profiteers from exploiting the drug distribution system by restricting availability and charging astronomical prices. Pharmacists, other health professionals, and patient groups must work with legislators and the Food and Drug Administration to remove restrictions that currently limit the extent to which affordable medications can be provided for patients.

Daniel A. Hussar

New Drug Review - *continued*

the binding of orexin A and orexin B to OX1R and OX2R receptors. Suvorexant is an orexin receptor antagonist and is the first medication with this mechanism of action. By blocking the binding of orexins to their receptors, it is thought to suppress the wake drive. Like the extended-release formulation of zolpidem (e.g., Ambien CR) and eszopiclone, it has been approved for the treatment of patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance. The effectiveness of suvorexant was evaluated in three placebo-controlled studies. The new drug was determined to be superior to placebo in reducing the time to sleep onset and in increasing total sleep time.

The antagonism of orexin receptors may underlie potential adverse events such as signs of narcolepsy and cataplexy, and loss of orexin receptors has been reported in humans with narcolepsy.

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