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Development of future indications for BOTOX®

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ABSTRACT

Since the late 1970s, local injections of BoNT have provided clinical benefit for patients with inappropriately contracting muscles with or without pain or sensory disturbance. Marketing authorization for some BoNTs, depending on country, include core indications of dystonia (blepharospasm and cervical dystonia), large muscle spastic disorders (not yet approved in the United States, e.g., adult post-stroke spasticity and equinus foot deformity), hyperhidrosis and aesthetic. Subsequent development has extended to selected conditions characterized by recurrent or chronic pain (migraine headache), and urologic indications (neurogenic/idiopathic overactive bladder; prostate hyperplasia), with multiple additional opportunities available. Portfolio management requires a careful individual opportunity assessment of scientific and technical aspects (basic science foundation, potential to treat unmet medical need, product-specific risk in specific populations, therapeutic margin/safety profile, and probability of successful registration pathway). This article describes ongoing development targets for BOTOX®.

1. Introduction

For over a quarter century, local injections of botulinum toxin type A (BoNTA) have provided clinical benefit for conditions with unmet need, characterized by inappropriately contracting muscles, with or without pain or sensory disturbance. Marketing authorization depends on the commercial product and country. For Allergan's specific formulation of botulinum toxin type A, BOTOX®, marketing approval includes core indications of dystonia (blepharospasm and cervical dystonia), axillary hyperhidrosis, and aesthetic enhancement. Other indications such as spasticity and equinus foot deformity are not yet approved in the United States, but are licensed in specific countries. Subsequent development has extended to certain conditions in which pain is the primary symptom (migraine headache) and urologic conditions affecting bladder control (neurogenic and idiopathic overactive bladder) and other urological indications with lower urinary tract symptoms such as benign prostate hyperplasia. Surgical options, including minimally invasive surgery are available, yet patients may prefer a pharmacological alternative to avoid possible complications of surgery.

The development of these and other indications is influenced by a variety of factors in the pharmaceutical and biological products industry, as well as current requirements of regulatory agencies worldwide. This chapter describes several examples of indications for which BOTOX® is currently in development: chronic migraine, overactive bladder, and benign prostatic hyperplasia, as well as some of the industry trends that influence portfolio management decisions.

2. Bio-pharmaceutical industry and regulatory trends

Biological and pharmaceutical product development is influenced by industry trends, as well as the regulatory environment. Economic factors heavily influence industry decisions, as each new biopharmaceutical costs more than

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$1 billion to develop (Tufts University, 2008). This high cost has been coupled with increased regulatory requirements related to safety and comparative efficacy data (Tufts University, 2008). As these are important areas of study, resource prioritization decisions must be made in product development.

Portfolio management requires a careful individual opportunity assessment of scientific and technical aspects such as basic science foundation, the potential to treat an unmet medical need, risk in specific populations, therapeutic margin/safety profile, and probability of successful registration pathway, which must be weighed against the potential return on R&D investment, including successful subsequent commercialization, competitive environment, and synergy with corporate product offerings. Published clinical studies document the utility of BoNTA in many different disorders and conditions, and it is challenging to determine which of these indications to pursue for licensure. In general, innovative new products must address an unmet medical need, add value over existing therapies, and demonstrate cost effectiveness. In the next section, we consider a few of the novel indications for which BOTOX® is currently under development.

3. Novel indications under development

3.1. Migraine

The beneficial effects of BoNTA on pain were noted as early as the 1980s, when Tsui and colleagues reported not only reduced muscle contractions and improved head position in cervical dystonia patients, but also substantial decreases in the disabling pain characteristic of this disorder (Tsui et al., 1985, 1986). Subsequent observations by our group indicated an even greater effect of BOTOX® on pain than motor function in cervical dystonia (Brin et al., 1987). In the early 1990s, several groups reported pain relief following BoNTA injections for the treatment of focal spasticity (Dengler et al., 1992; Memin et al., 1992). These findings were initially interpreted to indicate that BoNTA relieved pain secondary to muscle spasms. However, this explanation has since proven to be too simplistic, as the timing and magnitude of pain relief do not always parallel the reduction in muscle spasms. BoNTA is known to inhibit acetylcholine release from gamma motor neurons that innervate the intrafusal fibers in muscle spindles, which may alter sensory feedback and contribute to pain reduction (Rosales et al., 1996). However, a primary effect on the release of pain neuromodulators (e.g., substance P, calcitonin gene-related peptide [CGRP]) is probably important in the therapeutic effect (Aoki, 2005).

In the late 1990s, several groups reported that BOTOX® reduced pain associated with primary headache disorders (Binder et al., 1998, 2000; Schulte-Mattler et al., 1999). This led to many additional open-label and controlled trials of BOTOX® in various primary headache disorders (Aurora, 2006). Although most open-label studies report beneficial effects of BOTOX® on headache, significant improvements over placebo had not been convincingly demonstrated in controlled trials (Aurora, 2006). These trials have been characterized by large placebo effects and the allowance of concomitant prophylactic medications, which may have impacted the findings (Aurora, 2006).

Based upon the results of a series of phase 2 studies, Allergan is currently focusing its development efforts on the effects of BOTOX® in the treatment of chronic migraine. The phase 3 program consists of 2 large double-blind, placebo-controlled studies in migraine patients with headaches and/or migraines that occur on 15 or more days each month. The preliminary data are encouraging (Allergan, 2008) and the results from these studies will be available in 2009.

In phase 2 trials of BOTOX® for the treatment of migraine patients with headache on 15 or more headache days per month, the most frequent treatment-related adverse events (>5%) were muscular weakness, neck pain, neck rigidity, injection site pain, blepharoptosis, headache, shoulder/arm pain, hypesthesia, hypertonia, and dysphagia (only 225 U dose associated with dysphagia >5%), with headache and injection site pain consistently not significantly different from placebo (Mathew et al., 2005; Silberstein et al., 2005).

3.2. Urological indications

3.2.1. Traditional therapies

Urological conditions characterized by lower urinary tract symptoms are often under-reported and under-treated (Milsom et al., 2001; Wille-Gussenhoven et al., 1997). These may include lower urinary tract symptoms of voiding and storage of urine in the bladder as with benign prostate hyperplasia or symptoms focused on the bladder itself as in overactive bladder. Initial management strategies may consist of watchful waiting and behavior modification, followed by pharmacotherapy if symptoms worsen (Patel and Chapple, 2008).

Overactive bladder has now been recognized as an important medical condition leading to severe impairments of quality of life for the affected patients (Rovner and Wein, 2002). The incidence increases with age. Unfortunately, many patients experience only modest improvement with the available oral medications (Herbison et al., 2003) or are unable to tolerate them. Side effects such as dry mouth, cognitive dysfunction, memory impairment, constipation, and dizziness are particularly troublesome (Chancellor, 2007) – especially in the elderly – (Herbison et al., 2003; Klausner and Steers, 2007) and individuals with neurological disease often require higher doses for symptom management (Bennett et al., 2004; Denys et al., 2006).

For benign prostatic hyperplasia, oral medications include alpha blockers, which can be associated with postural hypotension, dizziness, and retrograde ejaculation (Emberton et al., 2008; Nickel et al., 2008), and 5-alpha reductase inhibitors, which are associated with loss of libido and sexual function (Nickel, 2006). Ultimately, these medications are associated with poor adherence due to inadequate efficacy and/or intolerable side effects (Kelleher et al., 1997; Nix and Carson, 2007).

Surgical therapy is another treatment option for patients with benign prostatic hyperplasia; however, in addition to potential surgical complications, incontinence, and sexual dysfunction may result (Meyhoff et al., 1984).