2019 Global Drug Delivery & Formulation REPORT

Part Two of a Four-Part Series

Part 1: A Review of 2019 Product Approvals

Part 2: Notable Drug Delivery and Formulation Product Approvals of 2019

Part 3: Notable Drug Delivery and Formulation Transactions and Technologies of 2019

Part 4: The Drug Delivery and Formulation Pipeline

By: Josef Bossart, PhD, Executive Editor, PharmaCircle LLC

Introduction

This is the fourth edition of the report's Notable Drug Delivery and Formulation Product Approvals, and the most challenging from an editorial perspective. In previous years, it was possible to identify 10, 20, or even 30 approvals that reflected a new or existing drug delivery technology in new or clinically important ways. That wasn't the case for 2019. While many products were approved using a variety of drug delivery and formulation technologies, very few qualified as notable. This year, we have decided to limit this section to four approvals.

Perhaps drug delivery has just been in a resting phase in terms of technology and novel product development for the past decade. Technology in general is marked with leaps and rests. When was the last time you really needed the technology benefits offered by a new computer, television, or microwave oven? The auto industry seems to be breaking out of a decades-long technology rest with self-driving and electric vehicles. Auto styles and colors may change annually, but for decades we were offered the same vehicles with a new design and a few more creature comforts. It seems to be the same with drug delivery technologies. What worked in 1985 still works in 2020, perhaps with somewhat better performance, but little else. The most exciting potential drug delivery technology of the past two decades, inhaled macromolecules, has largely failed and been supplanted by patient-friendly autoinjectors. Better, but not really notable in 2019.

The four selected products, using technologies developed as much as decades ago, provide insight into the future of therapeutics and business. Zolgensma, Novartis' gene therapy for the treatment spinal muscular atrophy is perhaps the first significant step in validating gene delivery and expression as a viable therapeutic option for simple genetic diseases. Janssen's Spravato is notable less for the nasal delivery technology than the elegance of its solution to a pressing medical need. Rybelsus, the first non-injectable macromolecule likely to achieve widespread use and commercial success may also close the door behind it, at least with this generation of macromolecule absorption enhancers. What's next? Aurora's High CBD Drops points to a parallel future when the increasing sophistication of botanicals competes directly with more traditional pharmaceutical products.

Is there a technology revolution sitting on a lab bench or in the clinic? That will be subject of the next two parts of this report. Let's appreciate for now what 2019 has delivered.

Spravato (Janssen Pharmaceuticals, Inc.)

Active: Esketamine HCl (274 Daltons, salt)
Molecule Type: Small Molecule
Indication: Treatment Resistant Depression
Delivery Route: Nasal
Dosage Form: Nasal Solution
DD Category: Nasal Spray Pumps/Devices
Dosing: Twice per Week, then Once per Week
First Approval: 2019-03-05 (USA)
Technology: Aptar BiDose Systems
Technology Owner: Aptar Pharma

Development Summary

The first evidence of Spravato clinical development is a Pre-IND meeting held with the FDA May 2012. Janssen-sponsored trials of intravenous esketamine, the s-isomer of the previously approved racemic ketamine, for treatment-resistant depression were initiated June 2012. The first intranasal studies with patients, pharmacokinetic studies, were initiated in the second half of 2013. Dosages for intranasal trials were agreed with the FDA in December 2014. The new drug application was filed September 2018, and approval was received March 2019. Overall development, from the time of first regulatory discussions to approval, was 6.8 years. The clinical and regulatory pre-NDA filing period was 6.3 years. Spravato is classified by the FDA as a new active ingredient rather than a new molecular entity.

Platform/Technology Summary

Aptar's BiDose nasal device is, as the name suggests, indicated for the administration of two doses, generally one dose in each nostril. The device can be used with both liquids and powders and is not primed before use. Maximum liquid volume is 0.1 ml, which is the case with Spravato. Dosing is two doses of 14 mg per nostril (two devices required). A total of six other products using the BiDose technology have been identified as in clinical development. The most advanced BiDose technology-based pipeline product is Milestone Pharmaceuticals' MSP-2017 (etripamil) in Phase 3 development.

Formulation Summary

Spravato is a water-based formulation with 28 equivalent milligrams of base esketamine hydrochloride (32.3 mg) in 0.2 ml. The excipients are citric acid, edetate disodium, sodium hydroxide, and sterile water for injection.

Reflections

From a drug delivery and formulation technology perspective, there is nothing remarkable about Spravato. The BiDose device offers a number of patient benefits but nothing evolutionary, much less revolutionary. The importance of Spravato rests with its ability to provide patients with a more convenient dosing option that can encourage treatment and compliance. The use of intravenous racemic ketamine for the treatment-resistant depression has achieved considerable popularity as an off-label use of the drug. Intravenous administration can vary from 5 minutes to 2 hours in a clinical facility setting. From a cost perspective though, intravenous ketamine may be a cheaper option for many patients given the $650 per dosing (two devices) price for Spravato, not including physician costs, about $32,000 per year. This compares with $400 or so for a single weekly or bi-weekly ketamine infusion session. Spravato forecasts vary widely from $600 million to $3 billion annually at peak.

Spravato may be a small step forward in drug delivery and formulation technology application, but it provides an important benefit for patients and the Johnson & Johnson bottom line.

Rybelsus (Novo Nordisk Inc.)

Active: Semaglutide (4,114 Daltons)
Molecule Type: Peptide Conjugate
Indication: Glycemic Control, Adults Type 2 Diabetes
Delivery Route: Oral
Dosage Form: Oral Tablet

DD Category: Oral Peptide/Protein/ Macromolecule Receptor Carrier
Dosing: Once Per Day
First Approval: 2019-02-20 (USA)
Technology: Eligen Technology
Technology Owner: Emisphere Technologies, Inc.

Development Summary

The first evidence of clinical development is a December 2009 safety and pharmacokinetic trial in healthy subjects. A series of safety, tolerability, and pharmacodynamic trials followed leading to efficacy and dose-ranging studies starting in 2016. The new drug application was filed with the FDA in March 2019 followed by approval September 2019. The time from the start of clinical activity to approval was 9.8 years, with 9.2 years spent in the clinical development stage.

Platform/Technology Summary

The Eligen technology has a long history with multiple product failures and a single marketed product, Eligen B12, approved as a medical food, prior to Rybelsus' approval. First announced in 1994, the Eligen technology has been previously applied without success to calcitonin and heparin. The partnership with Novo Nordisk related to GLP-1 Receptor Agonists goes back to 2008. There appear to be no additional Eligen-based products in active clinical development.

Formulation Summary

Rybelsus is approved as 3-, 7-, and 14-mg tablets with the Eligen absorption-enhancing excipient, SNAC. The approved dosage forms contain magnesium stearate, microcrystalline cellulose, kovidone, and salcaprozate sodium. All dosages use the same 300 mg of salcaprozate sodium. The product has a number of restrictive conditions related to dosing. The prescribing information requires Rybelsus to be taken 30 minutes prior to a meal. The meal is required, it is not an empty stomach requirement. Varying from the recommended dosing results in lower (meal too early) or higher (meal too late) absorption of the active. Bioavailability is stated as 0.4%-1.0%.

Reflections

Rybelsus represents the first true oral macromolecule targeted to a large patient group. The Eligen technology appears to be sufficiently efficient to allow for efficacy with an acceptable safety profile. The real magic here may be the manufacturing efficiencies that permits pricing to be on the order of the injectable despite a 1% bioavailability. Big Pharma is loath to compromise on margins, but with exclusivity in the oral GLP-1 market, a recent approval recommendation in Europe, the prospect of an obesity claim, and forecast annual sales exceeding $3 billion, a compromise on cost of goods is more than acceptable. For the Eligen technology, it seems that Emisphere hit the jackpot on its last nickel.

Zolgensma (AveXis, Inc, Novartis Pharmaceuticals Corp.)

Active: onasemnogene abeparvovec-xioi
Molecule Type: AAV9 Vector Based Gene Therapy
Indication: Spinal Muscular Atrophy (SMA)
Delivery Route: Injection, Intravenous Infusion
Dosage Form: Injection Suspension
Dosing (Duration): Single Infusion (One Hour)
DD Category: Adeno-Associated Virus Vectors, Brain Targeting
First Approval: 2019-05-24 (USA)
Technology: NAV Vectors, AskBio Self-Complementary Vector, Genethon AAV Vector
Technology Owner: Multiple

Development Summary

Clinical-stage development started with a Pre-IND meeting December 2011 followed by an IND submission August 2013. Patient trials were initiated in May 2014 with a gene transfer trial to evaluate safety and efficacy. The BLA was filed November 2018 and received a priority review. The time from first FDA interaction to approval was 7.4 years, including a 6-month review.

Platform/Technology Summary

As is the case with all gene and cell therapy products, Zolgensma depends on multiple technologies from multiple companies. The core underlying technology is based on the NAV Vector technologies, including AAV9, associated with the University of Pennsylvania and the laboratory of Jim Wilson. RegenXbio appears to hold an exclusive license to the NAV Vector platform. Developed in the early 2000s, there has been some recent frustration expressed that the current generation of AAV technologies have seen little advancement since then.

Formulation Summary

Zolgensma is provided as an injection suspension in 5.5-ml and 8.3-ml vials with a nominal concentration of 2.0×10^{13} vector genomes per ml. Excipients include Poloxamer 188 (0.005%), magnesium chloride (1 mM), Tris (20 mM), and sodium chloride (200 mM).

Reflections

Zolgensma has elicited significant medical, regulatory, and public attention as a result of its purported clinical benefits and high price, $2.1 million per patient. Despite the high price, there is health economics support for a price in excess of $1 million for this potentially life-transforming treatment. It will be interesting to see if Novartis can recapture the $8.7 billion it invested in purchasing AveXis, the developer of Zolgensma. There are only a limited number of infants born with the condition, about 1 in 10,000, and many fewer individuals, drug plans, and governments able to afford the $2.1-million price tag. The hope it seems is that the AveXis platform technology can be applied to additional indications with larger populations and similar pricing elasticity. Two identified AveXis projects, AVXS-201 for Rett Syndrome and AVXS-301 for ALS, were in preclinical development at the time of the last public announcement (2018). Zolgensma is currently being studied for intrathecal administration.

Aurora High CBD Drops (Aurora Cannabis Inc.)

Active: Cannabidiol (314 Daltons)
Molecule Type: Small Molecule
Indication: Severe Epilepsy
Delivery Route: Oral
Dosage Form: Oral Liquid (60mg/ml)
DD Category: Oil Formulations
Dosing: As Required
First Approval: 2019-12-02 (Ireland)
Technology: Not Described
Technology Owner: Aurora Cannabis

Development Summary

There is no clinical development information available, and there likely was no formal development beyond basic quality and stability studies. The product, a 60% w/v oil formulation of cannabidiol (CBD), was added to the Irish Medical Cannabis Access Programme in 2019. It is reasonable to expect the company was required only to provide composition and purity documentation.

Platform/Technology Summary

The Irish authorities and Aurora Cannabis offer little information in terms of the formulation beyond simple concentration information. Product information at the company's website for a similar product claims "no fillers or dilutive agents." Aurora Cannabis, operating in Canada where cannabis was legalized in 2019, sells CBD and THC in a variety of formulations, including Cannabis Oil, Softgels, Oral Dissolve Strips, Edibles, and Vaporizers.

Reflections

The Aurora High CBD Drops approval in Ireland is a high-profile example of how a number of jurisdictions are handling pseudo-pharmaceutical products. Aurora's product, without the clinical development and regulatory burden associated with formal drug approvals seems set to compete directly with GW Pharmaceuticals' Epidiolex, which was approved September 2019 in Europe. The Irish clinical guidance documents for the Cannabis for its Medical Use Access Programme explicitly note use for Dravet and Lennox-Gastaut syndrome, the Epidiolex- approved indications. From a pricing perspective, the Canadian consumer price for the Aurora product of about CDN $100/gram (~US $80), offers a 30% discount to the published US Epidiolex price of US $120/gram. The Irish pricing is not available.

Going well beyond the typical botanical type of preparation where plant material is dried, ground up, and offered as powders or stuffed into capsules, these pseudo-pharmaceuticals often go through significant processing, purification, and standardization before being compunded into a variety of dosage forms using drug delivery and formulation technologies. From an industry perspective, this may well be an indicator of future trends. With a sheen of validated efficacy, availability without a prescription or even a physician visit, and the aura of "natural," these standardized plant-based "therapeutics" will be irresistible to many consumers without drug plans, those who are suspicious of multinational pharmaceutical companies, and others who want to try a different approach to their condition.

The opportunity of pseudo-pharmaceuticals is validated by the number of these products with combined estimated annual sales of $40 billion. Cannabis companies are jumping on the opportunity of wider use of CBD and THC products by licensing and filing patents on a variety of delivery technologies to create their own proprietary dosage forms. And cannabis is not the only opportunity. A search for St. John's wort preparations online finds numerous dosage forms available, including capsules, tinctures, liquid capsules, topical oils, gummies, extracts, and teas, some of which are available as concentrated and extended-release presentations. There are even Kosher versions.

The Irish approval may well be validation of a global move toward non-prescription botanicals as first choice therapeutics. For consumers and governments, the price is right. For companies, the opportunity is attractive with very limited regulatory demands and a quick path to market. Do high-priced niche products like Spravato and Zolgensma define the future of the innovative pharmaceutical industry where good enough is good enough if the price is right? It seems the same old, same old, will no longer suffice to deliver enhanced patient benefits and sustained industry profitability.