Closer Look

MEMORANDUM

FDA approves MannKind's Afrezza for type 1 and type 2 diabetes; a victory for indefatigable Al Mann - June 27, 2014

Executive Highlights

- Today, the FDA announced the approval of MannKind's Afrezza in adult patients with type 1 or type 2 diabetes. The full prescribing information is posted here.
- Afrezza is not categorized, according to the label, as more rapid-acting than injected rapid-acting-analogs, though we believe the "real life" impression will be different. The label does not include formal hypoglycemia or weight advantage claims.

Today, the FDA announced the approval of MannKind's Afrezza in adult patients (18+ years) with type 1 or type 2 diabetes, a major win in our view for patients (many type 2 refuse to take traditional insulin), providers (many PCPs won't teach patients to inject), and all those developing new insulins (to see a positive regulatory response). The news comes more than two weeks before the July 15 PDUFA date (an extension from the original April 15 PDUFA date) - the early FDA vote is consistent with the enthusiasm from the drug's April 1 Advisory Committee, where panelists overwhelmingly supported Afrezza (a 13-1 vote in favor of approval for type 1 diabetes, 14-0 for type 2 diabetes). We believe that very strong provider and patient views given in an Open Panel Session made a clear difference.

The full prescribing information (35 pages) for Afrezza is posted here, and notably, MannKind already has the URL www.Afrezza.com up and running. It was encouraging to see the broad approval in patients with type 1 or type 2 diabetes - based on the FDA's perspective at the Advisory Committee, an approval in type 1 had originally seemed like a long shot, though the decisive afternoon vote must have changed the FDA's mind. However, the FDA's work on the label was surprising. Most important, Afrezza is not perceived by FDA as more rapid-acting than injected rapid-acting-analogs, an omission management said was expected because although researchers see it as one of the product's perceived key advantages, there was not a large study to show this to be the case. The label is based on a 12-patient study with "noisy" data, not the larger study MannKind typically uses in its presentations; the latter used the previous inhaler, so it was excluded - we understand why but think that study with the old inhaler still shed light on the compound.

In addition, the label's hypoglycemia and weight sections only show type 2 diabetes data comparing Afrezza to placebo (i.e., no benefit on either) - these sections ignore the more positive type 1 data, which suggested some meaningful hypoglycemia and weight benefits. As usual, we don't always think randomized controlled trials are the best to understand "real" life, since the placebo arm patients usually have a better life in the trial ("lots of love" as one of our favorite doctors puts it) than they do in reality. While overall, the FDA did not feel that MannKind had sufficient evidence to support these comparative claims for label purposes based on the studies used to approve Afrezza, other trials will ultimately be able to be constructed now that Afrezza is approved. That said, in the short term, the label doesn't bode well for an uncomplicated reimbursement story for the drug, particularly for type 1; we think most type 1 patients interested in Afrezza will want it as a complement for their current insulin, not a substitute.

As expected, Afrezza is contraindicated in patients with lung disease (asthma, COPD). Though a point of contention at the Advisory Committee, the label asks providers to perform a spirometry (FEV1) test for pulmonary function in all patients before starting Afrezza, after six months of therapy, and annually, "even in the absence of pulmonary symptoms." Though perhaps not too surprising (three month tests would've been worse), this is definitely an additional "hassle factor." We did not perceive any notable or surprising contraindications/populations excluded from using Afrezza apart from those noted above.

The FDA is requiring the following post-marketing studies, which struck us as fairly reasonable overall: (i) a clinical trial in pediatric patients; (ii) a clinical trial to evaluate the potential risk of pulmonary malignancy with Afrezza (also assessing cardiovascular risk and long-term pulmonary function); and (iii) two PK-PD glucose-clamp trials - one to characterize dose-response and one to characterize within-subject variability. The latter will be more robust than the aforementioned 12-patient trial and should help demonstrate an ultra-rapid-acting claim (assuming data are consistent with prior studies). Certainly, the size and cost of the cancer trial could be significant, though we're not sure of the details at this point - we aren't sure why that couldn't just be done with a registry but as always note that we do not have regulatory expertise.

Overall, despite the gaps on the label, the approval is a major win for patients and HCPs, who will now have access to an insulin that is easier to prescribe and take, more rapid-acting (despite what the FDA says, we believe it is faster than injected rapid-acting analogs), and better for hypoglycemia and weight (at least in type 1 diabetes and, we believe, in the "real lives" of type 2 patients). The approval is also a huge victory for MannKind following two complete response letters for Afrezza (one in 2010 and one in 2011). We have enormous respect for Al Mann, who at age 89 has persevered to get this product approved and has done something we've never seen at a CEO level - crossed from devices into drugs and proven a success. This is particularly notable given he could have easily walked away from work at all after selling Minimed to Medtronic for nearly $4.0 billion in 2001! While some would say the commercial marketplace will determine ultimate success for Afrezza, we believe many researchers and scientists and patient advocates would term Afrezza development and FDA approval alone success. The big questions for MannKind are how will patients, HCPs, and partners respond and what will reimbursement look like - the funds will determine who has access, who can try it, etc. Below, we discuss the prescribing information and medication guide in more detail.

- **"Despite the faster absorption of insulin (PK) from Afrezza, the onset of activity (PD) was comparable to insulin lispro."** Overall, the FDA does not categorize Afrezza as an "ultra rapid-acting" insulin that is faster than current rapid-acting analogs. Although this was disappointing to see given what we have read and heard - the faster profile has consistently been touted as a major advantage of the drug by key opinion leaders, patients in trials, and the company - given the data requested and used by FDA, this is perhaps not unexpected. Indeed, as we understand it, the study the FDA used for the "comparable" onset of action claim was only in 12 patients and resulted in "noisy" data (figure 3a, page 15 of the prescribing information). The study MannKind usually references in its presentations is a larger, more robust study that did show a more rapid-acting benefit, but it used the prior Gen 1 inhaler, so it was not considered by the agency - even though the compound itself hadn't changed. As we understand it, the FDA ultimately did not agree with the term "ultra-rapid" for labeling purposes, but the PK data still made it onto the label (see below), which is a win for MannKind. We have heard a great deal from researchers excited by the early data and believe the label will eventually be updated - from a reimbursement perspective, however, the gap here is a negative.
    - **The Humalog label, for comparison, has a clear claim for a more rapid-acting profile vs. human insulin:** "... Studies in normal volunteers and patients with diabetes demonstrated that Humalog has a more rapid onset of glucose-lowering activity, an earlier peak for glucose lowering, and a shorter duration of glucose-lowering activity than human regular insulin. The earlier onset of activity of Humalog is directly related to its more rapid rate of absorption." The Afrezza label contains no similar language, though we assume it could be incorporated following the post-marketing study.
    - **Fortunately, the mandated post-market PK/PD study is large enough that it should resolve the "ultra rapid-acting" issue.** At that point, the label could be revised if Afrezza demonstrates a much more rapid onset of action, consistent with prior studies. Certainly, reaching peak insulin concentration in the blood much more rapidly (see below) should have a corresponding beneficial effect on pharmacodynamics.

    - **Afrezza Pharmacodynamics:** The median time to maximum effect of Afrezza was approximately 53 minutes, and the effect then declined to near baseline levels by about 160 minutes. For context, the NovoLog label states, "the maximum glucose-lowering effect of NovoLog occurred between 1 and 3 hours after subcutaneous injection." The Humalog label does not have this language specifically.
    - **Afrezza Pharmacokinetics:** The maximum serum insulin concentration was reached by 12-15 minutes after inhalation of Afrezza 8 units and serum insulin concentrations declined to baseline by approximately 180 minutes.
    - **The Afrezza label instructs patients to take Afrezza "at the beginning of your meal,"** though the press release says it can be taken "at the beginning of each meal, or within 20 minutes after starting a meal." The range of patients taking insulin is broad; good HCPs will individualize advice on timing of insulin.

- **The "Hypoglycemia" section of the Afrezza label only includes data on Afrezza in type 2 diabetes, a major surprise** - the language is factual, though the numbers clearly suggest that Afrezza causes *more* hypoglycemia than the placebo comparator on the "non-severe" side (severe: 1.7% vs. 5.1%; non-severe: 30% vs. 67%). This is noise, and we look forward to "real life" data; in the meantime, from a reimbursement perspective, this is not a positive although "non-severe" hypoglycemia is not as important to payers (or anyone else) as severe hypos, given the downside. We were surprised not to see the hypoglycemia data from the phase 3 trial of Afrezza in type 1 diabetes, which suggested a significant hypoglycemia advantage for Afrezza vs. aspart: 9.8 hypoglycemic events per subject-month with Afrezza vs. 14 events with insulin aspart ($p<0.0001$), and eight events of severe hypoglycemia per 100 subject-months with Afrezza vs. 14 with insulin aspart ($p=0.10$, not significant officially, unless you're the patients experiencing the greater severe hypo).
- **Similarly, the weight gain section of the Afrezza label only uses type 2 diabetes data and is brief, only three sentences long!** The text suggests Afrezza causes more weight gain than placebo (+0.49 kg vs. -1.1 kg), again, very surprising in our view to use this comparator. In the phase 3 trial in type 1 diabetes, patients on Afrezza lost, on average, 0.4 kg (1 lb) relative to the 0.9 kg (2 lbs) gained with insulin aspart ($p=0.01$) - this was another key omission in our view.
    - **In addition, the Afrezza label's summary of the phase 3 trials of type 1 and type 2 diabetes only include A1c and fasting glucose data** - there is no mention of the weight or hypoglycemia results from the trials. This struck us as odd and perhaps a reminder of the FDA Drug Division's tendency to de-prioritize the value of secondary endpoints (weight, hypoglycemia).
- **Afrezza has been approved in blue and green cartridges, which "approximate" four and eight units of injected insulin, respectively.** This differs from what MannKind has said in the past, where the cartridges of Afrezza were said to approximate three- and six-units of injected rapid-acting insulin. The four-unit cartridge contains 0.35 mg of insulin, and the eight-unit cartridge contains 0.7 mg of insulin. That is a less narrow dosing than what we had expected and also not an advantage, especially for insulin-sensitive type 1 patients. Indeed, based on dosing as well as the label, we don't expect most type 1 patients to get reimbursement straight away, though the fact that they do have the option to get the insulin at all maybe perceived as a positive by some who were worried about outright approval.
    - **The prescribing information contains a fairly simple dosing table to guide patients and providers when starting Afrezza.** The table shows that Afrezza will likely be a challenging medication to dose in type 1 diabetes and in any patient that is insulin sensitive, as the ability to titrate is limited at low doses of insulin - we believe it may well be useful for corrections for very many patients, but that the blood glucose may need to be at a certain fairly high level to start (so that hypoglycemia doesn't ensue when treating hyperglycemia). For insulin resistant type 2 patients, the dosing change is a positive since fewer Afrezza doses are needed.

Injected Mealtime Insulin Dose	Afrezza Dose
Up to 4 units	4 units (one Afrezza blue cartridge)
5-8 units	8 units (one Afrezza green cartridge)
9-12 units	12 units (one blue, one green cartridge)
13-16 units	16 units (two green cartridges)
17-20 units	20 units (one blue, two green cartridges)
21-24 units	24 units (three green cartridges)

- **"Afrezza is not a substitute for long-acting insulin. Afrezza must be used in combination with long-acting insulin in patients with type 1 diabetes."** We wonder if this stipulation excludes type 1 patients on pumps from taking Afrezza, since technically they are not using "long-acting insulin." We do believe there will be demand by many type 1 patients to use Afrezza as a supplement to pumps for use as corrections - we look forward to testing this use soon ourselves. While some may not want to carry around another object, we believe some will if it gives them a chance to get rid of hyperglycemic episodes faster. We also think if there is good immediate feedback, the demand by type 1 patients will be high and payers may not battle the type 1 front so much since it is a limited number of patients and there is less "exposure" compared to type 2, where a very high number of patients could try to take the drug if it is shown to be easier to use.
- **"Afrezza has not been studied in pregnant women."** The FDA recommends the drug not be used during pregnancy unless the "potential benefit justifies the potential risk to the fetus."
- **The Afrezza inhaler can be used for up to 15 days from the date of first use.** After 15 days of use, the inhaler must be discarded and replaced with a new inhaler.
- **Afrezza will come packaged in six different cartridge configurations:**
    - 60 x 4 unit cartridges and 2 inhalers.
    - 90 x 4 unit cartridges and 2 inhalers.
    - 90 x 8 unit cartridges and 2 inhalers.
    - 90 cartridges; 60 x 4 unit cartridges and 30 x 8 unit cartridges and 2 inhalers.
    - 90 cartridges; 30 x 4 unit cartridges and 60 x 8 unit cartridges and 2 inhalers.
    - 180 cartridges; 90 x 4 unit cartridges and 90 x 8 unit cartridges and 2 inhalers.
- **Packages of Afrezza are supposed to be stored in the refrigerator (36-46 degrees Fahrenheit).** Once a foil package of Afrezza has been opened, patients are instructed to use it within 10 days. Before using, the cartridges and inhaler should be at room temperature for ten minutes.

Close Concerns Questions

Q: Why do the hypoglycemia and weight sections of the label only discuss the type 2 data?

Q: Will Afrezza eventually obtain a more-rapid-acting claim vs. current rapid-acting analogs?

Q: How will payers perceive the advantages of Afrezza for type 1 and type 2 diabetes? Will payers reimburse Afrezza as a "complement" for type 1s rather than a substitute for their current insulin?

Q: Could compelling adherence data be collected that would demonstrate significant advantages of Afrezza?

Q: How much of a hassle will pulmonary function testing be?

Q: How will potential partners perceive the Afrezza label? When will MannKind sign a partner?

Q: When is launch and what will roll out and marketing look like?

--by Adam Brown and Kelly Close