Evaluate Vantage

February 26, 2019

Xeljanz warning Jaks up safety concerns

Madeleine Armstrong

An increased risk of blood clots and death with Pfizer's drug could also bode ill for newer Jak inhibitors.

Safety has long been a worry with the Jak inhibitors, but the issue has reared its head again with an official FDA warning for Pfizer's Xeljanz. The news has reignited concerns about the entire class even as developers of newer Jaks, notably Abbvie and Galapagos, claim that their projects are safer than the first-generation drugs.

The picture with Abbvie's upadacitinib and Galapagos/Gilead's filgotinib should become clearer this year. The former is filed with the FDA for rheumatoid arthritis, with an approval decision expected in the third quarter. Meanwhile, Galapagos could report data any day from its Finch-1 and -3 phase III studies of filgotinib, also in RA.

Next generation

The theory is that more selective Jak blockers could be safer than the likes of Xeljanz and Lilly's Olumiant, which has also been dogged by adverse events.

However, in a possible sign that all is not well with the newer projects, Abbvie is only seeking approval in RA for the lower upadacitinib dose tested, 15mg. The project has been linked with thrombotic events, although later trial results have partly assuaged these worries. It is unclear whether upadacitinib will face an advisory committee.

Meanwhile, safety will be key when the Finch trials of filgotinib read out (*Upcoming events – Pivotal data for Galapagos and Cara, February 15, 2019*).

Xeljanz sales grew 32% to $1.8bn in 2018, so there is demand for the Jaks despite the safety risks. But more concerns over adverse events could hit this product and perhaps the whole class, which has so far attracted big forecasts.

Great expectations: sales forecasts for selected Jak inhibitors			
Project	**Company**	**Mechanism**	**2024e sales ($bn)**
Approved			
Xeljanz	Pfizer	Jak 1, 2 & 3 inhibitor	3.5
Olumiant	Lilly	Jak 1 & 2 inhibitor	1.3
Filed			
Upadacitinib	Abbvie	Jak 1 inhibitor	2.5
Phase III			
Filgotinib	Galapagos	Jak 1 inhibitor	1.1
Source: EvaluatePharma.			

Further safety issues could also put paid to Jaks in less serious autoimmune conditions such as alopecia, where several are in development, including Pfizer's PF-06651600 and Concert Pharmaceuticals' CTP-543 (*Upcoming events – Phase II readouts loom for Concert and Reata, September 21, 2018*).

Xeljanz warning

Yesterday's FDA warning on Xeljanz came after Pfizer last week reported an increase in pulmonary embolism and death in a postmarketing safety trial of Xeljanz in RA.

The safety signal was seen in patients receiving 10mg twice daily – twice the FDA-approved dose in RA. The trial is continuing with the 5mg twice-daily dose only, and is set to complete this year.

The 10mg twice-daily dose of Xeljanz is approved in another indication, ulcerative colitis, but this decision was controversial: an FDA advisory committee voted in favour of the higher dose despite question marks over its long-term safety. At the time, Leerink analysts suggested that bowel disease doctors might be more willing to accept a risk of toxicity in return for an option for hard-to-treat patients.

The warning might not put a big dent in Xeljanz's sales, as ulcerative colitis is only a small part of the drug's 2024 forecast, at $511m. But, after a long list of safety issues with Jak inhibitors, it provides another reason to be cautious.