Evaluate Vantage

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New Nuplazid use in limbo after US knockback

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Acadia becomes the latest to fall foul of the US FDA's apparently increasingly strict stance.

Recent changes at the US FDA appear to have led to the agency becoming strict with sponsors. Following a surprise adcom for Fibrogen/Astrazeneca's roxadustat and a review of accelerated approvals that has led to the withdrawal of several cancer drugs' uses, Acadia has now come up against an apparently emboldened regulator.

The company last night suffered a setback for Nuplazid in dementia-related psychosis. The agency has not gone so far as rejecting the antipsychotic for this new use, but instead has "identified deficiencies" that are preventing labelling discussions. The upshot is that Nuplazid looks unlikely to get the go-ahead in this setting by its April 3 Pdufa date, and might not get approved here at all.

For its part, Acadia seemed frustrated by the FDA's approach during a conference call last night, with executives saying the agency had not given any details on the nature of the deficiencies.

The company also provided a timeline on Nuplazid's filing in dementia-related psychosis, noting that the FDA had confirmed twice that an adcom was not needed, and that it was on track to communicate with Acadia by March 3, the day that discussions on labelling and post-marketing requirements had been due to start.

Efficacy or safety?

It is therefore difficult to gauge what the problem is, but Stifel analysts guessed that it might be down to Acadia's data package. The filing was backed by just one phase III trial in dementia-related psychosis, Harmony, which evaluated relapse prevention, as well as the phase II 019 study in Alzheimer's disease psychosis. The analysts questioned whether there was enough evidence of Nuplazid's acute benefit, and raised the possibility that the FDA might require another acute efficacy trial.

Alternatively, the issue might be safety. Nuplazid is already approved for treating hallucinations and delusions associated with Parkinson's disease psychosis, but its label contains a black-box warning spelling out the increased risk of death in elderly dementia-related psychosis patients treated with antipsychotics.

Either way, Stifel now believes that a complete response letter is likely. In contrast, Leerink analysts are confident that Nuplazid still has a future in dementia-related psychosis.

Investors seem unconvinced of the drug's chances, with Acadia's stock opening down 44% this morning. Dementia-related psychosis is a much bigger market than Parkinson's disease psychosis – 10 times bigger,

according to the company. *EvaluatePharma* sellside consensus puts 2026 sales of Nuplazid in Alzheimer's at $1.4bn, versus $1.0bn in Parkinson's.

Next up?

The broader question for biopharma is whether recent regulatory developments do indeed reflect a change in the FDA's standards. If Acadia is to be believed and this latest communication really did come out of the blue, it might be the case that something has shifted and that the agency, after years of apparent leniency, is finally baring its teeth.

It is ironic that this apparent transformation has coincided with Janet Woodcock's stint as acting commissioner. She is famous for pushing for the approval of Sarepta's controversial Duchenne muscular dystrophy drug Exondys 51, despite the lack of a placebo-controlled trial.

One company that might be feeling particularly nervous at the prospect of a new, fiercer FDA is Biogen, whose Alzheimer's candidate aducanumab is now due an approval decision by June 7, after a recent three-month extension to its review.

Stifel noted that aducanumab data are arguably "more questionable" than the Nuplazid results in dementia-related psychosis, but added that the major amendment employed in the case of adu was "optically very different" from the agency's communications with Acadia.

The FDA itself has been very positive on adu while its advisory committee was not, making the ultimate outcome for the drug difficult to call. But, if the agency is intent on regaining its bite, Biogen investors should be wary.