Evaluate Vantage

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Shedding light on Intercept’s opaque disclosure

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Intercept’s woes have continued as a possible new liver toxicity signal was buried in a regulatory filing. What could this mean?

Intercept last week added to its woes after a sharp-eyed investor noticed that modified boilerplate language in the company’s quarterly filing implied further toxicity problems for Ocaliva. The revelation, missed by all the sellside, knocked 8% off the company’s already battered stock price last week.

Without further information about the precise toxicities that the US FDA has apparently been looking into since May it is impossible to quantify the possible problem, but the safety database Advera Health Analytics sheds important light on the matter. Meanwhile, during a major biotech boom, Intercept stands off 68% on the year.

The group’s big knockback, of course, occurred in June when the FDA handed Ocaliva a complete response letter for Nash, apparently citing concerns that activity based on a surrogate histopathologic endpoint might not outweigh potential risks (*The dream is over for Intercept, June 29, 2020*).

Deeper problems

Already the risk of hepatobiliary events was known, casting doubt over whether Ocaliva’s label would be extended from its narrow approved use in primary biliary cholangitis (PBC) to a broad indication like Nash. However, the latest problems suggested that the problems were deeper still.

In last week’s 10-Q filing Intercept slipped out the fact that the FDA had “begun to evaluate a newly identified safety signal regarding liver disease for Ocaliva ... as a potential risk”. Remarkably, this review had begun in May, but had not been mentioned publicly until now.

Advera, which gets its data from the FDA’s FAERS adverse event reporting system and adjusts for a number of factors to add context and remove duplication, shows several active liver toxicity signals not already cited on Ocaliva’s label.

Most frequently reported adverse events for Ocaliva in the hepatobiliary system organ class				
Adverse event	**US label status**	**Cases (primary)**	**ROR***	**Event type**
Chronic hepatic failure	Not labelled	6	18.21	Serious
Bile duct stenosis	Labelled	7	11.56	Serious
Portal hypertension	Not labelled	12	8.87	Serious
Cholangitis acute	Labelled	3	6.26	Serious
Hepatic cirrhosis	Labelled	33	5.62	Serious
Hepatic failure	Not labelled	61	5.47	Serious
Hepatic fibrosis	Labelled	9	5.35	Serious
Bile duct stone	Labelled	8	5.12	Serious
Hepatorenal syndrome	Not labelled	6	5.08	Serious
Hyperbilirubinaemia	Labelled	18	4.52	Serious
Autoimmune hepatitis	Not labelled	6	1.83	Serious
*Note: *risk odds ratio. Source: Advera Health Analytics.*				

These include liver failure and portal hypertension, all derived from adverse event reporting from in-market use of Ocaliva for PBC.

In terms of frequency of these events, the relevant metric is the risk odds ratio (ROR). An ROR score above 1 indicates a higher than expected reporting rate for a given adverse event, and while there is no widely accepted benchmark regarding the level triggering a safety signal many in the industry assume that results above 2.0 warrant attention, Advera says.

One caveat is that all of these issues could be related to the underlying disease, since PBC affects the liver, but the higher the ROR the less likely it seems that this would explain away the adverse event seen.

Whatever the reason for Intercept not mentioning the FDA review until last week, the fact that this started in May fits chronologically with the Nash adcom postponement. Investors will now want to know whether the new toxicity signals were behind the June CRL, and whether they presage further restrictions on Ocaliva's approved PBC indication; the label already has a black boxed warning.

But the bigger opportunity in Nash is most at risk. For now the sellside remains incredibly bullish, with 2026 consensus at $2bn, according to *EvaluatePharma*, even with mounting evidence that this drug is not going anywhere fast.

Intercept's regulatory disclosure timeline for Ocaliva (obeticholic acid)	
Date	**Note**
May 2016	Approved in primary biliary cholangitis
Feb 2018	Black box warning added to PBC label regarding hepatic decompensation and failure when Ocaliva was dosed more frequently than recommended
Nov 2019	FDA accepts filing in Nash, Pdufa set for Mar 26, 2020
Dec 2019	FDA sets adcom for Apr 22, 2020; Pdufa expected to be extended
Feb 2020	Pdufa extended to Jun 26, 2020
Mar 2020	FDA reschedules adcom for Jun 9, 2020
May 2020	Adcom postponed to accommodate review of additional data requested by the FDA
Jun 2020	Received CRL for Nash
Aug 2020	10Q filing reveals that in May the FDA had begun to evaluate a newly identified safety liver disorder toxicity signal as a potential risk
Expected early Q4	*Type A meeting for Nash*
Source: company filings.	