Natpara sails through panel despite headwind; NPS Pharma gets an 8-5 'yes' vote in hypoparathyroidism

By Randy Osborne
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With briefing documents and history on its side, the biologic license application for NPS Pharmaceuticals Inc.'s Natpara emerged with success from a meeting of the FDA's Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) as expected, scoring eight votes in favor of approval and five against – but a handful of panelists said their ballots might have gone either way.

NPS' recombinant human parathyroid hormone (PTH) for the potentially fatal disorder hypoparathyroidism, if approved, would be the first therapy cleared for U.S. marketing in that indication. Lee Weinstein, acting chief of the metabolic diseases branch of National Institute of Diabetes and Digestive and Kidney Diseases in the National Institutes of Health (NIH), voted for approval.

"I would honestly say I was very much on the fence with this, and perhaps at another time or another moment, I could have made my vote the other way," he said, adding that he "was not overly impressed with the study that was done and some of the outcomes that were shown in the data. To be honest with you, as a physician, I think I would probably very rarely if ever even prescribe it." Still, he said, there appear to be a "small number of very difficult-to-treat patients that, for whatever reason – and I'm not sure we totally understand why that is" – are helped by the drug.

Thomas Weber from Duke University Medical Center went the other way, despite "compelling stories from patients" during the public-hearing portion of the meeting because he wanted to see a "true reduction in urinary calcium" and better assurance that patients would not meet with renal complications. "In the absence of clear benefit, the bar for safety has to be much higher," he said.

Panelists considered data from the pivotal trial called REPLACE, along with supportive outcomes from RELAY and RACE. NPS, of Bedminster, N.J., disclosed positive top-line results from REPLACE in late 2011. There was another study, too, smaller and single-center, called REPEAT, that didn't play much of a role. (See *BioWorld Today*, Nov. 8, 2011.)

EMDAC verified expectations from briefing documents that questions would have mostly to do with the risks of such problems as hypo/hypercalcemia, hypercalciuria, and osteosarcoma with long-term use.

Members seemed frustrated that many of their questions could not be answered in REPLACE data. In an intent-to-treat analysis, NPS reported that 53 percent (48/90) of Natpara-treated patients achieved the primary endpoint vs. 2 percent (1/44) of placebo-treated patients ($p < 0.0001$).

That endpoint was defined as a 50 percent or greater reduction in oral calcium supplements and active vitamin D therapy, along with a total serum calcium concentration that was normalized or maintained compared to baseline after 24 weeks of treatment.

Not using calcium excretion as the primary endpoint bothered panelists such as Weber, while others said the trial was necessarily too small to capture the volume of data that would be required with a different primary goal. Others questioned the dosing regimen, wanting more frequent than once per day; one voter suggested an administration route other than an injection. "This drug would be perfect if it was a pump, or at least multiple-day dosing, but that's not the option that was put in front of me today," said the NIH's

Natpara was well tolerated in REPLACE. Thirteen of the 134 randomized subjects discontinued the study early, including seven on placebo. Overall, the incidence of adverse events and serious adverse events was similar in both groups.

The good data were bolstered by EMDAC's past, as surveyed by Leerink Partners analyst Joseph Schwartz, who found the most recent 2.5 years voting history showed nine of 10 meetings ended with a positive vote. The meetings included two orphan drugs and eight mass-market indications. Since early 2013, the only negative EMDAC meeting involved Vascepa (icosapent ethyl), the lipid-lowering agent from Amarin Corp. plc, of Dublin. (See *BioWorld Today*, Oct. 17, 2013.)

With Vascepa, the picture was nothing like that with Natpara. Not only were the briefing documents much more doubtful, but also the market for mixed dyslipidemia is much larger. What's more, the FDA "was (and still is) attempting to address a political question regarding special protocol assessments (SPA) and the emergence of new, conflicting information," Schwartz wrote in a research report. For the first time ever, the committee turned down an application submitted under an SPA agreement. (See *BioWorld Today*, Oct. 18, 2013.)

The issue at hand, though, was Natpara, for which analysts had predicted a win at EMDAC, with Schwartz – who maintained an "outperform" rating and $40 price target on the stock – pegging peak sales in 2025 of $1 billion. More conservative on the shares was Jefferies analyst Eun Yang, with a "hold" rating and a target price of $26. NPS (NASDAQ:NPSP) stopped trading at a price of $32.70 for the day of the panel meeting.

Yang pointed out that the clinical significance of Natpara-induced osteosarcoma in a preclinical rat model was unknown, similar to the PTH peptide Forteo (teriparatide, Eli Lilly and Co.) in osteoporosis. "It remains to be seen whether the FDA would place a black box for osteosarcoma in Natpara label (as a PTH class effect) and consider treatment duration limitation to less than two years, similar to Forteo (and Preotact [also from NPS] previously) despite the chronic nature of secondary hypoparathyroidism. The osteosarcoma matter cropped up in the EMDAC meeting, with panelists proposing risk evaluation and management strategies if the compound is approved.

Last year, NPS regained full worldwide rights to Gattex (teduglutide) for short bowel syndrome and the recombinant PTH Preotact from Takeda Pharmaceutical Co. Ltd., of Osaka, Japan, in exchange for stock valued at $50 million, plus a milestone payment of $30 million in cash or stock in the first year that net sales of both products exceed $750 million. (See *BioWorld Today*, March 20, 2013.)