COWEN AND COMPANY

Emerging Company Research

Hyperion Therapeutics — Initiating With Outperform (1)

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Ravicti Helps The Medicine Go Down

Analysts
Phil Nadeau, Ph.D.
(646) 562-1336
phil.nadeau@cowen.com

Nicholas Bishop, Ph.D.
(646) 562-1378
nicholas.bishop@cowen.com

Summary: Hyperion is focused on the development of treatments in the areas of orphan disorders and hepatology. Hyperion's lead candidate Ravicti is for the chronic management of ammonia levels in patients with a urea cycle disorder (UCD). Ravicti has succeeded in four Phase II and III trials, and is on file with at the FDA with an October 23, 2012 PDUFA date. Ravicti has been shown to be at least as potent as the current standard of care, but with much better tolerability and dosing convenience. Our consultants expect Ravicti to be approved based on its current filing, and for it to quickly capture majority share of the UCD market. Based on Ravicti's potential in UCD alone, we think Hyperion is significantly undervalued, and are initiating coverage with an Outperform rating.

- **An IPO That Will Soon Have Product Sales?!?** Hyperion is unique among its biotech IPO peers because it will almost certainly have revenue by H1:13. Hyperion owns an option to purchase Medicis' currently marketed UCD franchise Buphenyl and Ammonul. Hyperion will exercise that option with near certainty during H1:13. We project that those marketed products and Ravicti will generate nearly $50MM in revenue in 2013, growing to $125MM in 2016. We project Hyperion will be modestly profitable in 2013, and generate $40MM+ in net income in 2014.

- **UCD Provides N-T Cashflow, Hepatic Encephalopathy L-T Upside Potential.** Based on its superior profile, our consultants expect Ravicti will largely replace Buphenyl in the UCD market, and also expand the market modestly. We therefore view Ravicti as a relatively low risk $100MM+ opportunity that should drive Hyperion to sustainable profitability. Ravicti has produced intriguing Ph. II data in hepatic encephalopathy (HE), a potential $1B market. Ravicti could enter Ph. III in HE in 2013. While the HE oppy contains more development and commercial risks, our consultants are optimistic that Ravicti will be able to find a path to market.

HPTX(08/17)	**$10.04**
Mkt cap	**155.6MM**
Dil shares out	15.5MM
Avg daily vol	26.8K
52-wk range	$10.0-12.0
Dividend	Nil
Dividend yield	Nil
BV/sh	NA
Net cash/sh	$3.03
Debt/cap	6.0%
ROE (LTM)	NA
5-yr fwd EPS growth (Norm)	NA
Price Target	
S&P 500	**1418.2**

Revenue$MM

FY Dec	2011 Actual	2012E Prior	2012E Current	2013E Prior	2013E Current	2014E Current	2015E Current
Q1	—	—	0.0	—	—	—	—
Q2	—	—	0.0	—	—	—	—
Q3	—	—	0.0	—	—	—	—
Q4	—	—	0.0	—	—	—	—
Year	**0.0**	**—**	**0.0**	**—**	**49.8**	**103.5**	**114.0**
EV/S	—	—	—	—	2.3x	1.1x	1.0x

EPS$

FY Dec	2011 Actual	2012E Prior	2012E Current	2013E Prior	2013E Current	2014E Current	2015E Current
Q1	—	—	1.14A	—	—	—	—
Q2	—	—	(0.60)	—	—	—	—
Q3	—	—	(0.50)	—	—	—	—
Q4	—	—	(0.43)	—	—	—	—
Year	**3.34**	**—**	**(2.51)**	**—**	**0.30**	**2.15**	**2.15**
P/E	—	—	—	—	33.5x	4.7x	4.7x

Investment Summary

Hyperion is focused on the development of treatments in the areas of orphan disorders and hepatology. Hyperion's lead program includes a suite of products to treat urea cycle disorders. Urea cycle disorders, or UCDs, are a constellation of diseases in which the body lacks the ability to clear ammonia, a byproduct of protein digestion. Approximately 2,000 people in the United States have a UCD, and just over 500 are receiving pharmacotherapy. If left untreated UCDs can cause learning disabilities, mental retardation, and even death. Hyperion owns an option to purchase the leading FDA-approved therapy for the chronic management of UCDs, Buphenyl, and will begin marketing it by mid-2013. While Buphenyl can rescue patients from death, it has an excessive pill burden, a foul taste, and causes GI side effects in most patients. Hyperion has developed Ravicti to replace Buphenyl. Ravicti has succeeded in four Phase II and III trials, and is on file at the FDA with an October 23, 2012 PDUFA date. In a pooled analysis of all four studies, Ravicti has been shown to have significantly better ammonia control compared to Buphenyl. More important, Ravicti has far superior palatability in a dramatically reduced drug volume (1 tablespoon or less) with few GI side effects, making it much more tolerable for patients. Our checks suggest that Hyperion will successfully transfer the vast majority of treated UCD patients from Buphenyl to Ravicti over the next few years and we project it will achieve $100MM+ in sales by 2016. Outside of UCD, Ravicti has shown intriguing Phase II data in Hepatic Encephalopathy (HE), a potential $1B market. Hyperion expects to meet with FDA by YE:2012 to define Ravicti's future HE trials. We believe that Hyperion is undervalued based on Ravicti's potential in UCD, without any contribution from other indications. Today we are initiating coverage with an Outperform rating.

Urea Cycle Disorders Are Orphan Conditions That Can Be Fatal If Untreated

Patients with a urea cycle disorder lack the ability to clear ammonia, a byproduct of protein digestion, from their bodies. Ammonia is a significant neurotoxin that is particularly damaging to the developing brain, and if left untreated UCDs can lead to mental retardation and death. In fact, before treatments were available, the five year survival for an infant diagnosed with the condition was only 22%. Hyperion and the UCD registry estimate that there are 2,000 patients with clinically-evident urea cycle disorders in the U.S. today, with about 30 new cases per year. Of those, about 1,000 are diagnosed, and just over 500 are on pharmacotherapy.

We Expect Hyperion's Ravicti To Replace The Current Standard Of Care Buphenyl

The majority of urea cycle disorder patients must take Medicis' Buphenyl chronically to keep their plasma ammonia levels under control. Physicians say that Buphenyl has revolutionized the treatment of UCDs as it can protect patients' intelligence, and allow them to live a normal lifespan. However, most patients are not satisfied with Buphenyl. Nearly all patients experience gastrointestinal side effects that can be very severe. Moreover, Buphenyl is difficult to take, and can require up to 40 pills per day. The pill burden and side effects can be so bad that some infants require a G-tube to get the drug.

Hyperion has developed Ravicti to replace Buphenyl. Ravicti has succeeded in four Phase II and III trials. In those studies Ravicti was shown to have at least as good

ammonia control as Buphenyl, and in fact trended toward better control in all trials. More important, Ravicti is far better tolerated, and is much more convenient. Ravicti is dosed via one tablespoon of nearly tasteless and odorless liquid, and causes few GI side effects.

Based on the accumulated data from Ravicti's clinical trials, our consultants are convinced that Ravicti is safe and effective, and expect the FDA to approve it on or around its October 23 PDUFA date. Moreover, they note that all patients in their practices in the Ravicti trials vastly preferred Ravicti to Buphenyl, and therefore expect Hyperion will be able to transfer most Buphenyl patients to Ravicti.

Hyperion To Own The Major UCD Therapies By H1:2013

Hyperion purchased all of the worldwide rights to Ravicti from Medicis in March of 2012, and has an option to purchase the other two approved UCD therapies Buphenyl and Ammonul from Medicis during H1:13. Hyperion expects to exercise the option, bringing all three UCD therapies under its roof. Given that all three therapies have historically been owned by Medicis, we expect the H1:13 purchase will be given FTC clearance. Hyperion will promote all three via a 20-person specialty salesforce. Based on the focused nature of the market, and the orphan pricing model that Hyperion expects to apply to Ravicti and Buphenyl, we project that Hyperion's UCD business will be profitable shortly after Ravicti's FDA approval.

Ravicti Has Produced Intriguing Data In A Second Condition, Hepatic Encephalopathy

Hepatic Encephalopathy (HE) refers to a condition of worsening brain function resulting from a buildup of toxins in the blood due to a failure of the liver to remove them. HE can potentially occur secondary to a variety of disruptions in normal liver function, but etiology of chronic HE most commonly involves cirrhosis due to alcohol abuse or hepatitis infection. The disease is quite prevalent; according to the U.S. Department of Health and Human Services' Healthcare Utilization Project (HCUP), up to 340,000 U.S. patients may suffer from overt episodic HE. Hyperion is hopeful that Ravicti's systemic, ammonia-selective mechanism of action may prove useful in preventing HE events, with potentially superior and/or complementary efficacy vs. available agents. Hyperion has successfully completed Phase I and II testing for Ravicti in HE, and plans to move into Phase III, pending an end of Phase II meeting with the FDA in Q4:12. We believe Ravicti could yield $300MM+ in sales in HE, if successfully developed.

Hyperion Appears Undervalued Based On Our Projections For Ravicti In Urea Cycle Disorders Alone

Based on our checks, we think that Hyperion should be able to successfully transfer the vast majority of treated UCD patients from Buphenyl to Ravicti over the next few years. We model 2013 – 2016 Ravicti sales of $13MM, $60MM, $85MM, and $110MM, respectively. Our total UCD franchise projections are $49.8MM, $103.5MM, $114MM, and $124.5MM for 2013-16, respectively. With limited commercial infrastructure necessary to promote the UCD franchise, we project that Hyperion will be profitable and sustainably cash flow positive beginning in 2014. Importantly, our P&L model includes no assumptions for Ravicti in HE. Nonetheless, based solely on our UCD estimates, our DCF analysis (see p. 21) concludes that Hyperion is substantially undervalued.

Upcoming Hyperion Milestones

Event	Timing
Ravicti's U.S. PDUFA date	October 23, 2012
Presentation of Ravicti's Phase II HE data at AASLD	November 2012
End Of Phase II meeting with FDA to discuss Ravicti in HE	Q4:12
HPTX to exercise option to purchase Buphenyl, Ammonul from MRX	H1:13
Ravicti's U.S. commercial launch	H1:13
Potential initiation of Ravicti's pivotal trials in HE	2013

Source: Cowen and Company

Hyperion Quarterly P&L ($MM)

	2011A	Q1:12A	Q2:12E	Q3:12E	Q4:12E	2012E
Ravicti						
Buphenyl						
Ammonul						
License and Other						
Total Revenue	-	-	-	-	-	-
COGS						
Gross Margin						
R&D	17.2	8.9	3.0	3.1	3.2	18.2
SG&A	8.9	2.3	2.5	2.8	3.1	10.7
Other						
Operating Expenses	26.2	11.2	5.5	5.9	6.3	28.9
Operating Income / (Loss)	(26.2)	(11.2)	(5.5)	(5.9)	(6.3)	(28.9)
Interest and other income, net	(3.3)	(0.7)	(0.8)	(0.8)	(0.8)	(3.1)
Pretax net income	(29.4)	(11.9)	(6.3)	(6.7)	(7.1)	(32.0)
Taxes						
Tax Rate						
GAAP Net Income	(29.4)	(11.9)	(6.3)	(6.7)	(7.1)	(32.0)
GAAP EPS	**$ (3.34)**	**$ (1.14)**	**$ (0.60)**	**$ (0.50)**	**$ (0.43)**	**$ (2.51)**
Diluted Shares Outstanding (MM)	8.8	10.4	10.5	13.5	16.6	12.8

Source: Cowen and Company

Hyperion Annual P&L ($MM)

	2011A	2012E	2013E	2014E	2015E	2016E
Ravicti	-	-	13.3	60.0	85.0	110.0
Buphenyl	-	-	32.5	35.0	20.0	5.0
Ammonul	-	-	4.0	8.5	9.0	9.5
License and Other	-	-	-	-	-	-
Total Revenue	-	-	49.8	103.5	114.0	124.5
COGS	-	-	3.4	8.6	10.4	12.2
Gross Margin			*93%*	*92%*	*91%*	*90%*
R&D	17.2	18.2	19.3	22.0	24.0	24.5
SG&A	8.9	10.7	21.5	25.0	27.5	28.0
Other	-	-	-	-	-	-
Operating Expenses	26.2	28.9	44.2	55.6	61.9	64.7
Operating Income / (Loss)	(26.2)	(28.9)	5.7	47.9	52.1	59.8
Interest and other income, net	(3.3)	(3.1)	(0.5)	(2.2)	0.0	4.0
Pretax net income	(29.4)	(32.0)	5.2	45.7	52.1	63.8
Taxes	-	-	-	2.5	7.8	19.1
Tax Rate	-	-	-	*6%*	*15%*	*30%*
GAAP Net Income	(29.4)	(32.0)	5.2	43.2	44.3	44.7
GAAP EPS	**(3.34)**	**(2.51)**	**0.30**	**2.15**	**2.15**	**2.15**
Diluted Shares Outstanding (MM)	8.8	12.8	17.0	20.1	20.6	20.8

Source: Cowen and Company

Ravicti To The Rescue In Urea Cycle Disorders

Urea cycle disorders, or UCDs, are conditions in which the body can not clear ammonia, a byproduct of protein digestion. Approximately 2,000 people in the United States have a UCD, 1,000 are diagnosed, and just over 500 are receiving pharmacotherapy for the condition. If left untreated UCDs can cause learning disabilities, mental retardation, and death. Hyperion owns an option to purchase the only FDA-approved therapy for the chronic management of UCDs, Buphenyl, and will begin marketing it by mid-2013. While Buphenyl can rescue patients from death, it has an excessive pill burden, a foul taste, and causes GI side effects in many patients. Hyperion has developed Ravicti to replace Buphenyl. Ravicti has succeeded in four Phase II and III trials, and is on file with at the FDA with an October 23, 2012 PDUFA date. Our checks suggest that Ravicti should be approved by the FDA, and that Hyperion should be able to successfully transfer the vast majority of treated UCD patients from Buphenyl to Ravicti over the next few years. We model 2013 – 2016 Ravicti sales of $13MM, $60MM, $85MM, and $110MM, respectively. Our total UCD franchise projections are $49.8MM, $103.5MM, $114MM, and $124.5MM for 2013-16, respectively.

Deficiencies In The Urea Cycle Lead To Disease

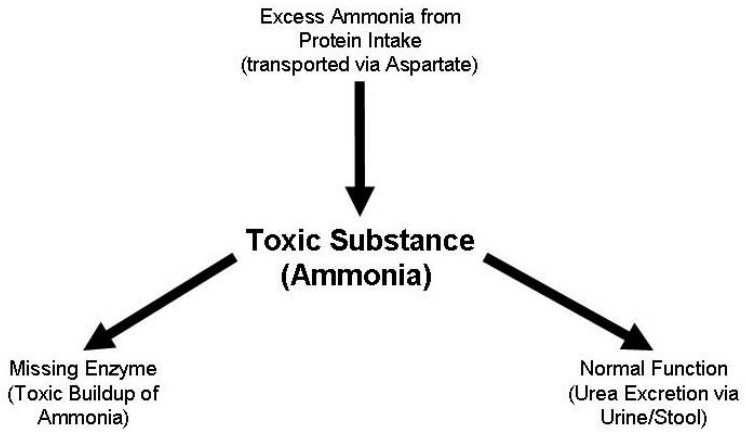
Originally discovered in 1932, the urea cycle is a series of five biochemical reactions that take place in the liver and kidney. It is the primary means by which the body is rid of highly toxic ammonia, a byproduct of protein ingestion in the intestines. Over the course of the reactions, ammonia is converted into urea, which is eliminated. There are five enzymes involved in the urea cycle: N-Acetylglutamatesynthetase (NAGS), Carbamoyl phosphate synthetase I (CPS1), Ornithine transcarbamylase (OTC), Argininosuccinic acid synthetase (ASS), Argininosuccinase acid lyase (ASL), and Arginase (ARG). As there is no known alternative pathway in the body for the synthesis of urea, a complete loss of function in any one of the enzymes is fatal. The UCDs are caused by partial deficiencies in the activity of any one of the enzymes, most often due to genetic defects. An inefficient urea cycle produces an accumulation of ammonia in the blood, a condition known as hyperammonemia. Ammonia is a significant neurotoxin that is particularly damaging to the developing brain. While the mechanism of neurotoxicity is not known for sure, the prevailing theory is that elevated levels of glutamine, formed from NH_4^+ and glutamate, produce osmotic effects leading directly to brain swelling. In early stages, patients with hyperammonemia have psychiatric disturbances, movement disorders, and episodic vomiting. As the duration of increased ammonia progresses, patients can become lethargic, experience seizures, and progress to coma and even death.

Patients with a UCD are detected either via newborn screening or clinical presentation. Currently, screening can only detect UCDs that result from the deficiencies in three of the enzymes, and in total these forms of UCD account for a minority of UCD cases. Our physician consultants estimate that one-quarter to one-half of UCD patients are detected through newborn screening.

The majority of patients first present with the clinical symptoms of hyperammonemia. The populations most affected are neonates, infants, and children, dependant on the dysfunctional enzyme. In circumstances where toxic levels of ammonia are greatest (i.e. a defect in CPS1), lethargy and periodic vomiting become evident within days of life. In the face of persistently elevated blood ammonia levels, coma and irreversible brain damage may soon follow. Infants, a particularly susceptible population, can develop permanent brain damage and/or

death within days after birth depending on the levels of hyperammonemia. Once a UCD is suspected, clinical tests are available to identify which enzymes are defective by gauging serum levels of the reactants (NAGS - Ammonia; CPS1 - Ammonia; OTC - Ornithine, Uracil, Orotic acid; ASS - Citrulline; ASL - Citrulline, Argininosuccinic acid; ARG – Arginine).

Overview of the Urea Cycle



Source: Cowen and Company

UCDs Produce Significant Morbidity, Mortality And Long Term Consequences

In the years before effective strategies were developed, the urea cycle disorders were fatal for the majority of patients. In a report of 216 patients with UCDs (1978 to 1995), 92 patients were followed, including a group who presented as newborns. The five-year survival was 22 and 41% for the neonatal and late-onset UCDs, respectively. While strategies to lower serum ammonia levels have improved mortality rates, in many cases UCDs still produce many life-long neurological or psychological problems, including developmental delay, intellectual disability (mental retardation), learning problems, speech disorder, attention deficit hyperactivity disorder, cerebral palsy, and seizure disorder. In fact, studies in the literature suggest the majority of UCD patients who first present as neonates will have diminished intelligence.

Urea Cycle Disorders Are Ultra-Orphan Conditions

Estimates of the incidence of urea cycle disorders vary in the medical literature, from 1:8200 live births to 1:25,000 live births. However, many patients are never diagnosed and/or have disease manifestation that is likely too mild for treatment. Additionally, some patients with a severe form can be cured by liver transplantation. Hyperion and the UCD registry estimate that there are 2,000 patients with clinically-evident urea cycle disorders in the U.S. today, with about 30 new cases per year. Of those, about 1,000 are diagnosed, and just over 500 are on pharmacotherapy.

Current Chronic Treatments Include Diet Modification, Liver Transplant And Buphenyl

The goal of treatment is to lower the amount of ammonia accumulated in the blood, thereby preventing the hyperammonemic crises and resulting neurological complications. Strategies include a protein-restricted diet, liver transplantation, and Buphenyl.

As ammonia is a by-product of the digestion of protein in the gut, most patients are put on a low protein diet. The composition of the diet will vary from patient to patient. Management of the diet is complicated, and the amount of protein tolerated by a patient is determined empirically by titrating against blood ammonia levels. Each patient's diet must be recalibrated frequently by monitoring growth, clinical status, and protein consumption. Physicians and patients must be careful not to over-restrict protein intake, as it can stunt growth and reduce quality of life. Moreover, if a patient does not consume enough protein, it leads to catabolism of the patients muscle tissue, which, ironically, increases the amount of ammonia in the blood. Conversely, patients who consume too much protein can have too much ammonia in the blood due to the digestion of protein in the intestine, leading to a hyperammonemic crisis. Diets often contain low-protein formula that provides nutrients and essential amino acids lacking nitrogen. Unfortunately, our consultants report that adherence with such diets is poor, and few patients maintain sufficient control of blood ammonia levels on diet alone.

Approximately one-quarter of patients diagnosed with UCD, typically the most severely affected patients, will receive a liver transplant. A successful liver transplant will restore the patients' ability to remove ammonia from the blood via the urea cycle, and therefore is curative. Patients are typically over 3 months of age, as the transplantation of younger patients results in more complications and reduced survival. However, liver transplantation can not reverse any pre-existing neurological damage, and therefore can not be conducted too late in life, either. Transplantation is generally recommended before the age of 1 year.

Other strategies for the treatment of UCD are to supplement enzyme deficiencies with necessary reactants allowing for formation of water-soluble, nitrogen-containing compounds that can be excreted, resulting in additional removal of ammonia. Arginine supplementation is helpful in all types of UCD deficiencies except arginase deficiency. Arginine deficiency results in a catabolic state that stimulates further mobilization of nitrogen from protein breakdown. In OTC, ASS, and ASL deficiency, arginine is needed to generate urea cycle intermediates, including ornithine, citrulline, and argininosuccinic acid. In OTC or CPS deficiency, small oral doses of citrulline are provided because of the theoretical advantage of incorporating aspartate nitrogen for clearance as urea in disorders upstream of ASS. Lastly, Carbaglu (Carglumic acid) was approved by the US Food and Drug Administration in March 2010, for treatment of hyperammonemia due to NAGS deficiency. Carglumic acid activates the first enzyme of the urea cycle (CPSI), leading to rapid reduction of plasma ammonia to normal levels. It is used for both acute and chronic hyperammonemia due to NAGS deficiency. Our consultants suggest Carbaglu is very effective, but NAGS is a relatively rare for on UCD, accounting for only approximately 3% of cases.

Our consultants suggest that a relatively small minority of patients are eligible for transplant, or adequately managed by diet and amino acid supplementation alone. Therefore the majority benefit from ammonia-lowering pharmaceuticals.

Ammonul Is For Acute Treatment Of Crises

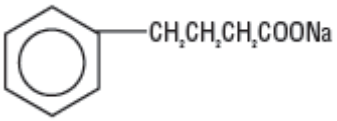
Approved in 2005, Ammonul is a combined preparation of sodium phenylacetate-sodium benzoate administered by intravenous delivery that functions to scavenge ammonia by creating an alternate pathway for excretion of nitrogen precursors. Ammonul administration forms water soluble products which are excreted in urine and requiring adequate renal function is essential. Ammonul is used in the hospital to quickly reduce ammonia levels in a patient in an hyperammonemic crisis. It is not used for the chronic management of UCD patients. Hyperion estimates that Ammonul currently sells about $8MM/year.

Buphenyl Is The Only Drug Approved For The Chronic Management Of Urea Cycle Disorders

The urea cycle removes the nitrogen of ammonia from the body by converting it to urea, which is excreted in urine. While this is the only means by which the body has to remove nitrogen and ammonia, other biochemical pathways are possible. Medicis/Hyperion's Buphenyl (sodium phenylbutyrate, NaPBA) creates a second biochemical pathway for the body to remove nitrogen/ammonia from the blood. Buphenyl is a pro-drug that is oxidized to phenylacetate (PAA). PAA conjugates with glutamine, forming phenylacetylglutamine (PAGN), which is removed in the urine. PAGN contains 2 molecules of nitrogen like urea, so functions as a urea alternative to remove the excess nitrogen/ammonia from the blood.

Buphenyl received FDA approval in 1996 and is indicated "as adjunctive therapy in the chronic management of patients with urea cycle disorders involving deficiencies of carbamylphosphatesynthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinicasicsynthetase (AS)." It is indicated for patients with both neonatal and late-onset forms of the disease.

Buphenyl Chemical Structure



Source: Buphenyl Prescribing Information

Our consultants prescribe Buphenyl to the majority of their UCD patients. The only patients who don't get it are those cured by prior liver transplant, the most mildly affected patients, and patients with NAGS who are cured by Carbaglu. Hyperion estimates that there are about 425 patients on Buphenyl in the United States today. Our consultants are generally satisfied with Buphenyl's ability to control blood ammonia levels, and they believe that when used as prescribed in conjunction with a low protein diet it can generally keep patients' blood ammonia levels in an acceptable range. In fact, they note that its ability to reduce blood ammonia levels and reduce the chances of a hyperammonemic crisis has saved the lives and neurological abilities of innumerable patients.

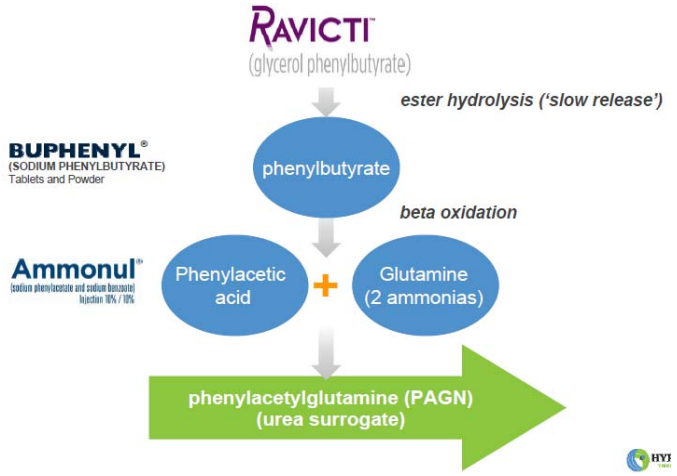
Unfortunately, Buphenyl's tolerability and pill burden are problematic, which leads to significant noncompliance and puts patients at risk for hyperammonemic crises. Our consultants suggest that their patients have several complaints about Buphenyl. First, they say its taste is bad. They describe it as foul and lingering. Second, the drug burden is excessive, with adult patients on a full dose requiring 20 grams. This

necessitates patients consume about 40 rather large pills. The dosing is frequent, administered 3 – 6 times per day. Third, Buphenyl, by the fact that it is sodium phenylbutyrate, includes a large sodium dose. Our consultants suggest that these issues combine to produce upper gastrointestinal tract side effects like gastritis, esophagitis, and GI pain in nearly all patients. The tolerability is so bad that young children will often fight against the administration of the drug, requiring the implantation of a G-tube. Our consultants suggest that overall one-quarter or less of there patients find Buphenyl reasonably tolerable, and take it with few complaints or issues.

Hyperion's Ravicti Is An Improvement Over Buphenyl

Hyperion's Ravicti (Glycerol phenylbutyrate, GPB, or HPN-100) is a pre-pro-drug of phenylacetate. It consists of a glycerol backbone with three phenylbutyrate molecules joined via ester linkage. As a prodrug of Buphenyl, it is metabolized into the active formulation and functions to diminish the ammonia levels in serum. Unlike Buphenyl (sodium phenylbutyrate), Ravicti includes no sodium, is nearly odorless and tasteless, and can be given in a much smaller volume. Therefore it offers much improved convenience and tolerability. Moreover, because an ester hydrolysis is required to release the phenylbutyrate, Ravicti's pharmacokinetic profile suggests it could be better at reducing ammonia levels throughout the day and night.

Ravicti's Place in the World



Source: Hyperion Pharmaceuticals

Ravicti Has Been Tested In 4 Key Studies In UCD

Ravicti's development in UCD includes 4 key studies, 2 Phase II and 2 Phase III, and their extensions, as well as 2 Phase I studies.

Ravicti's UCD Clinical Program

Study	Phase	Population	N
UP-1204-003	Phase II	Adults: Ages >18 yrs	13
HPN-100-005	Phase II	Pediatric: Ages 6 through 17yrs	11 (6 additional in extension phase)
HPN-100-006	Phase III	Adults: Ages > 18 yrs	46
HPN-100-007	Phase III	Pediatric: Ages 29 days through 5 yrs	15

Source: Cowen and Company

Two Phase I studies were conducted: a randomized, cross-over, open label study design used to assess safety, tolerability, and pharmacokinetic equivalence in healthy test subjects (001) and an open label study of the safety and PK equivalence in patients with cirrhosis but no hepatic encephalopathy (002). In the 001 study, patients were given Ammonul and HPN-100/GPB (formulated) or Buphenyl and HPN-100/GPB (unformulated). In this study, twenty-one adverse events were reported by 10 subjects while receiving Buphenyl compared with six receiving GPB. No serious adverse events were reported and the most significant AEs reported were dizziness (n=5), Headache (n=4), and nausea (n=3) with minor reports of epigastric discomfort and vomiting. In 002, there were no SAE and AEs were reported in 26/32 patients. While four subjects were notable for thrombocytopenia, the rest of the AEs were more subjective and vague in nature (i.e. GI complaints and headache). Collectively, the two studies suggested Ravicti exhibits adequate safety, achieves steady-state plasma concentrations within four days or less, and exhibit slow release characteristics.

Positive Phase II Data…

The first Phase II trial, UP-1204-003, was conducted in adult patients aged 18 and older with a diagnosis of UCD and who were on a stable dose of Buphenyl before enrollment. The trial was an open-label switchover study to compare Ravicti to Buphenyl. The trial enrolled 13 adult patients, and 10 completed. After enrollment patients continued to receive their Buphenyl dose for 7 days, and they were then admitted to a clinical trial site for overnight observation and 24-hour urine collection and pharmacokinetic and ammonia measurements. The patients were then switched to Ravicti. They took Ravicti for 7 days, and were then re-admitted to the clinical trial sites for the same suite of measurements. Results of the trial were published by Lee and colleagues in the July 2010 issue of *Mol Genet Metab*.

The data were solid, demonstrating that Ravicti was at least as good at removing ammonia as Buphenyl, with a similar, if not better, safety profile. Ten of the enrolled patients completed the study. There were 21 adverse events reported for 7 patients on Buphenyl, compared to 15 adverse events reported in 5 patients while on Ravicti. Nearly all adverse events on Buphenyl (19/21) and Ravicti (13/15) were mild. Two patients reported hyperammonemic crisis while on Buphenyl that were categorized as SAEs; no patients on Ravicti experienced hyperammonemic crises. Other notable AEs include a mental status change in a patient on Buphenyl that was classified as moderate, an abdominal distension in a patient on Ravicti considered severe, and a case of flatulence while on Ravicti considered moderate. Neither the flatulence nor the abdominal distension required treatment before resolving.

Ravicti trended toward better ammonia control. Ammonia values were approximately 30% lower on Ravicti compared to Buphenyl, with the time normalized area under the curve ammonia values of 26.2 for Ravicti, and 38.4 for

Buphenyl. While 39.6% of the ammonia values were above the upper limit of normal for ammonia while subjects were on Buphenyl, only 27% were while patients were on Ravicti. These differences were largely attributed to lower overnight ammonia values for patients on Ravicti. Exposure to phenylacetic acid (PAA, 575 vs. 596 µg*h/mL) and phenylacetylglutamine (PAGN, 1098 vs. 1133 µg*h/mL) were similar.

Following the adult Phase II trial, Hyperion conducted a second Phase II trial in children ages 6 through 17 years. This pediatric Phase II included two phases: a two-week, open label switchover comparison study similar to the adult Phase II, and a 12 month safety extension. The switchover portion of the trial enrolled 11 patients, while the extension phase enrolled 7 more. Data from the randomized switchover portion of the study were published in 2011 (*Mol Genet Metab.* 2011 Aug; 103(4) 323-9). All 11 patients in the switchover phase completed the trial. Ravicti again demonstrated noninferiority in its ability to control ammonia levels, demonstrating a trend toward superiority in the intent to treat analysis (95% CI 0.575, 1.061; p=0.102), and the trend reached statistical significance in a per-protocol analysis (95% CI 0.516, 0.958; p<0.05). The ratio of mean ammonia values (Ravicti:Buphenyl) was about 0.76. No hyperammonemic crises occurred while patients were on either Buphenyl or Ravicti.

The safety of the two agents was comparable. Adverse events possibly related to drug were reported in 2 subjects on Buphenyl, and 4 subjects on Ravicti. All were mild, except for one moderate adverse event of vomiting in a Ravicti patient that was assessed as not drug related and due to a coincident illness. The mild adverse events on Buphenyl were lymphadenopathy, decreased appetite, and cardiac murmur, while those on Ravicti were upper abdominal pain, ear and upper respiratory tract infection, and dermatitis contact. In the trial there was a trend toward higher PAA and PAGN exposure while on Ravicti (25% and 35%, respectively). The difference was not statistically significant, although this could have been due to the small sample size. PAA blood levels are a concern as the infusion of PAA in cancer patients has been shown to produce neurological toxicity. However, the levels achieved in cancer patients (499 – 1285 µg/mL) were far above those found in pediatric patients in this study (Cmax 90.5 µg/mL).

Interestingly, each patient was asked on day 14 whether they preferred Buphenyl or Ravicti, and all 11 chose Ravicti.

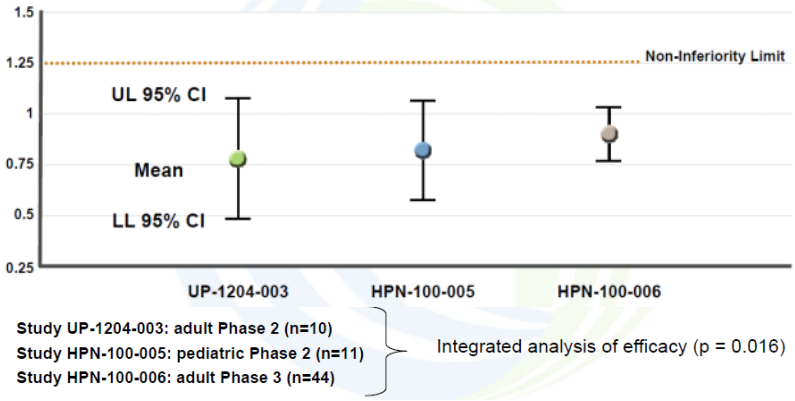
…Set The Table For Success In Phase III

Ravicti's adult Phase III trial was conducted in 46 UCD patients aged 18 years and older. Hyperion received an SPA for the trial. The study was a four-week, double-blind, placebo-controlled cross-over trial in which patients received Ravicti and Buphenyl for two weeks each. The primary endpoint was the non-inferiority of Ravicti to Buphenyl in blood ammonia control, assessed as 24-hour area under the curve on days 14 and 28 (the last day of each two-week treatment period). The non-inferiority margin in the trial's SPA was 1.25, meaning that the upper 95% confidence interval of ammonia on Ravicti could not be more than 25% higher than that seen on Buphenyl. Patients were to be on a stable dose of Buphenyl before enrolling, and in the trial they were to receive Buphenyl at their prescribed dose. They were given Ravicti at a dose that would deliver the same amount of PBA. Buphenyl and Ravicti were administered three times per day with meals, and the patients' diets were strictly controlled. All patients who completed the switchover part of the study were eligible to enter a 12-month, open-label extension study.

Of the 46 adults enrolled, 45 received at least one dose of study drug, and 44 completed the study. The mean daily dose was 13.49g or 7.55g/m^2 for Ravicti and 13.95g or 7.8 g/m^2 for Buphenyl. The trial met its primary endpoint, with ammonia levels for patients on Ravicti of 34.7 µmol/L, compared to 38.4µmol/L for patients on Buphenyl. The 95% confidence intervals for Ravicti relative to Buphenyl were 0.799 – 1.034, below the pre-defined non-inferiority margin in the SPA (1.25). In addition to the trend toward lower mean ammonia levels for patients on Ravicti, there was also a trend toward lower Cmax for patients on Ravicti compared to Buphenyl, 60.9 vs 70.8µmol/L, respectively.

Following the completion of the Phase III, Hyperion conducted an integrated analysis of the 2 Phase II's and the adult pivotal Phase III. In the 65 patients from the three trials, Ravicti produced statistically significantly better ammonia control than Buphenyl, p = 0.016.

Ratio of Mean Ammonia Values: (Ravicti: Buphenyl)



Source: Hyperion Pharmaceuticals

No deaths occurred during the Phase III trial, and there were no clinically meaningful changes in ECGs or laboratory values for either therapy. There was one hyperammonemic crisis during the trial in a patient on Buphenyl, and one Buphenyl patient withdrew early because of high ammonia levels accompanied by a headache. There was at least one adverse event reported by 23 patients on Buphenyl and 27 on Ravicti. The most common adverse events reported on Buphenyl were dizziness, headache, nausea, diarrhea, dyspepsia, and abdominal discomfort. The most common adverse events reported by patients on Ravicti were diarrhea, flatulence, headache, vomiting, fatigue, decreased appetite, and abdominal pain.

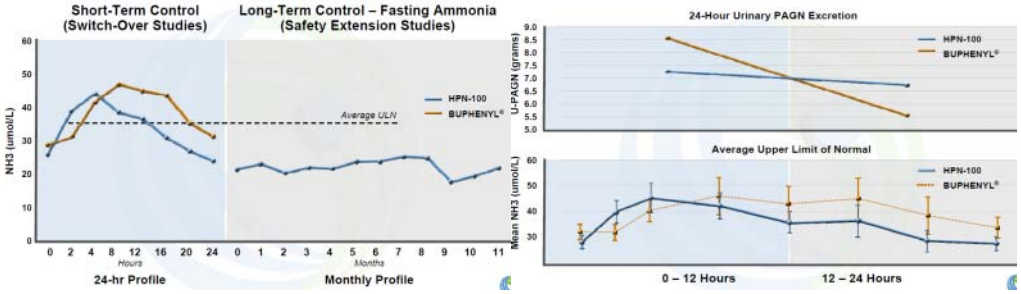
Extension Studies Demonstrate Long-Term Safety and Efficacy Of Ravicti

Patients who completed the adult Phase III, the pediatric Phase III, or the pediatric Phase II were eligible to enroll open-label extension studies. Of the 44 patients in the adult Phase III, 40 enrolled in the extension study. The 11 patients in Ravicti's pediatric Phase II continued onto the extension phase. Certain patients who did not complete the trials but met the enrollment criteria were eligible for the open-label safety studies. In total 77 adult and pediatric patients enrolled in the two 12-month open-label safety studies, and 69 completed. After exiting the open-label extension studies, patients could enter in the continued access protocol, and Hyperion currently has approximately 70 enrolled.

Hyperion has released combined data from the open-label studies. Through 12 months Ravicti continued to demonstrate a durable effect on ammonia control, with consistent blood ammonia values of 20-25 umol/L throughout the 12 months, below the 35 umol/L upper limit of normal.

During the 12 month extension phase patients had 40% fewer and HA crises compared to the 12 months before enrollment (when patients were on Buphenyl). Moreover, neuropsychological evaluations at baseline and after 12 months of treatment with Ravicti showed evidence of improvements in executive function among the pediatric patients ages 6 – 17. Functions improved include behavioral regulation (flexibility, inhibitory control) and metacognitive skills (goal setting, planning, self-monitoring).

Short- and Long-term Ammonia Control And Slow Release Behavior for Extended Maintenance of Plasma Concentration



Source: Hyperion Pharmaceuticals

FDA's Concern Over PAA Levels Prompts Phase III In Patients Under the Age of 6

When phenylbutyrate, the active ingredient in both Ravicti and Buphenyl, undergoes beta oxidation, phenylaceticacide (PAA) is produced. The formation of PAA is necessary for Ravicti and Buphenyl to remove ammonia from the body. PAA reacts with glutamine (which donates ammonia), forming PAGN, which is excreted from the body, removing the incorporated ammonia. However, in prior trials in cancer patients, the infusion of high levels of PAA has been shown to cause neurotoxicity at plasma concentrations ranging from 499 to 1285 μg/mL.

The metabolism and elimination of Ravicti and Buphenyl increases with body surface area, and consequently pediatric patients have higher PAA levels than adult patients. In the adult Phase II, the PAA Cmax following treatment with Ravicti was 40.5 ug/mL, while in the pediatric Phase II in children between the ages of 6 and 17 PAA Cmax was 90.5 ug/mL. Moreover, Ravicti's pediatric Phase II trial found that plasma levels of PAA were about 25% higher for Ravicti than Buphenyl (Cmax of 90.5 ug/mL vs 75.1 ug/mL).

During Hyperion's pre-NDA meeting, the FDA expressed concerns over the association between very high PAA levels with neurotoxicity. While the levels at which PAA has been associated with neurotoxicity are beyond the Cmax's recorded in Ravicti's trials, it is known that PAA levels can vary by as much as 10-fold over the course of a day, and therefore it excursions into the neurotoxic ranges could not be ruled out. Hyperion believes this concern has been harbored by the FDA since the initial cancer publications, and wasn't prompted by any of Ravicti's clinical data.

Nonetheless, in order to answer these concerns Hyperion accelerated the conduct of a pediatric Phase III trial.

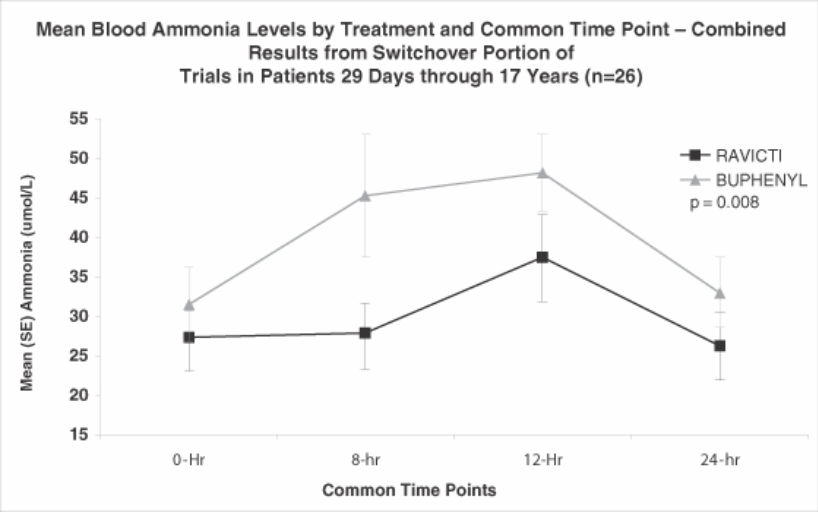
During H2:11 Hyperion initiated a Phase III in 15 pediatric UCD patients aged 29 days through 5 years. The trial is similar to the pediatric Phase II in patients aged 6 through 17 years in that it includes an open-label Buphenyl to Ravicti switchover. After enrollment patients continued to receive their Buphenyl dose for 7 days, and they were then admitted to a clinical trial site for overnight observation and 24-hour urine collection and pharmacokinetic and ammonia measurements. The patients were then switched to Ravicti. They took Ravicti for 7 days, and were then re-admitted to the clinical trial sites for the same suite of measurements. Following the switchover portion patients enrolled in a 12-month open-label extension study.

Detailed data from switchover portion of the study have not been released, although were submitted to the FDA in April 2012. Hyperion has disclosed that ammonia "tended" to be lower on Ravicti compared to Buphenyl among the 15 pediatric patients who enrolled in and completed the switchover part of the study. Moreover, based on the pharmacokinetic analysis of the study, Hyperion believes that PAA levels are similar for Ravicti and Buphenyl, and that PAA levels reflect age related differences in body surface area.

In its S-1 Hyperion has disclosed a post-hoc analysis of the pooled ammonia data from the two pediatric studies in patients aged 29 days through 18 years. In this pooled analysis, total daily ammonia exposure was significantly (p=0.008) lower in patients on Ravicti compared to patients on Buphenyl.

On PAA levels, Hyperion has released aggregate data from an integrated analysis of all pediatric patients between 29 days and 17 years. Hyperion found no relationship between adverse events and PAA levels. Average levels were well below the region of concern observed in the cancer trials, and in fact, of the 26 patients ages 29 days – 17 years in the studies, only one had a transient maximum PAA level over 500 ug/mL, and that was a 2 month old patient on Buphenyl. We believe this data strongly suggests the PAA levels produced by Ravicti are unlikely to lead to adverse events.

Ammonia Levels In Pediatric Patients



Source: Hyperion's S-1

A 12-month extension portion of the study continues, with data expected during Q2:13.

Rat Carc Findings A Wild Card, But We Think There Is A Compelling Case As To Why Unlikely Trip Up Approval

A standard part of the development program for any new medicine is nonclinical (conducted in animals) genotoxicity and carcinogenicity studies to assess its tumorigenic potential and the relevant risk to humans. For Ravicti the genotoxicity studies included Ames and chromosomal aberration assays testing Ravicti and its metabolites PBA, PAA, PAG, and PAGN. These studies showed that Ravicti and its key metabolites are negative for genotoxicity. The carcinogenicity studies included single dose oral toxicity studies in rats and monkeys, repeat dose studies of up to 13 weeks in mice, 26 weeks in rats, and 52 weeks in monkeys. A transgenic mouse carcinogenicity assay and a 2-year rodent carcinogenicity study were also completed. In the 6-month transgenic mouse study and the non-human primate studies, Ravicti was not found to be tumorigenic. Unfortunately, Ravicti did cause tumors in the 2-year carcinogenicity study in rats. Hyperion assembled a panel of expects who concluded that the rat findings do not suggest any real cancer risk in humans. The experts produced a position paper stating their conclusion.

In the 2-year rat carcinogenicity study, increases in the incidence of spontaneously occurring tumors were seen in the adrenal cortex, pancreas, and thyroid in both sexes, and additionally in the uterus, cervix, and Zymbal's gland in females. The scientific advisory panel made several important observations. First, a majority of the findings are rodent specific with no relevant counterpart in humans. The panel suggests that the findings represent "an aberrant response by the normal non-supplemented animals to sustained pharmacologically mediated metabolic alterations at the high exposures at the top dose levels." Second, the panel calculated exposure margins, and found that the male tumors occurred at >16x the human dose, and the female tumors occurred at >29x the human dose. The panel believes that these margins are sufficient to mitigate risk to humans. Last, the panel notes Ravicti and Buphenyl release the exact same chemical entity into the systemic circulation, and Buphenyl has never been associated with increased tumor risk. Based on these points, the panel concludes that the findings are unlikely to suggest risk to patients or to have any clinical relevance.

While it is impossible to know for certain how the FDA will deal with such findings, we are hopeful that they will not delay Ravicti's approval. We think the fact that Ravicti and its metabolites were negative for genotoxicity, and the fact that tumors were not found in mice, transgenic mice, and monkeys even with extended dosing, suggests the findings are likely idiosyncratic to rats. Moreover, we suspect the FDA will be comforted by Buphenyl's long-term safety track record, and the fact that Buphenyl and Ravicti are essentially the same active drug (PBA) once in the circulation. Moreover, the total number of people likely to ever be on Ravicti in UCDs is quite low – we estimate at peak about 600-700 people will be on Ravicti. Obviously everyone on Ravicti will have a serious medical condition, and the consequences of not adequately managing it are dire. We therefore are hopeful that the FDA will conclude that Ravicti is very unlikely to cause tumors, and that its risk-benefit is very positive, despite the rat findings.

Ravicti's U.S. Filing Has An October 23, 2012 PDUFA Date

Following the completion of Ravicti's adult Phase III trial, on December 23, 2011 Hyperion filed for FDA approval of Ravicti. This initial NDA requested an indication for the chronic management of urea cycle disorder patients ages 6 and above. The filing was granted an October 23, 2012 PDUFA date. Following the completion of the efficacy portion of Ravicti's pediatric clinical trial in patients aged 29 days through 5 years, in April 2012 Hyperion submitted a study report to the FDA on the trial, and submitted a revised draft package insert that now requested approval of Ravicti for patients as young as 29 days.

With Ravicti's PDUFA about 2 months away, it is increasingly unlikely that the FDA will review the filing at a Advisory Committee. Hyperion management has not been informed whether a panel will be necessary. However, given the time it takes for the FDA to convene a panel, and the notice that the FDA is required to give the company, one would expect that the FDA would have already notified Hyperion had it planned to hold a panel.

Hyperion Purchased Ravicti From Medicis, Will Purchase Buphenyl During H1:13

Medicis obtained its urea cycle disorder franchise via the purchase of Ucyclyd Pharma in 1999. Hyperion signed a collaborative agreement in 2007 with Ucycld/Medicis for Ravicti that included rights to purchase Buphenyl and Ammonul. Following a dispute between Medicis and Hyperion, the agreement was restructured in March 2012. At that time, Hyperion purchased all of the worldwide rights to Ravicti for an upfront payment of $6MM. Hyperion will pay Medicis a mid-to-high single digit royalty on Ravicti sales, regulatory milestones on the approval of Ravicti in indications outside of urea cycle disorders, and sales milestones.

In addition, Hyperion obtained an option to purchase Buphenyl and Ammonul from Medicis. The option can be exercised for a period of 90 days beginning on the earlier of the date of FDA approval of Ravicti for the treatment of UCD, and June 30, 2013, but in no event earlier than January 1, 2013. During H1:13 Medicis will pay Hyperion $0.5MM per month that Ravicti is not approved. Hyperion has indicated that it will exercise this option at the first opportunity. Hyperion will make a $22MM upfront payment to Medicis, plus future milestones and royalties. Hyperion can fund the purchase via a loan from Medicis that is payable over 8 quarters. When Hyperion exercises its option, Medicis will have the option to retain Ammonul for a price of $32MM. If Medicis retains Ammonul, the price of Buphenyl for Hyperion is reduced to $19MM, meaning that Medicis will need to make a net payment to Hyperion of $13MM.

Hyperion Expects To Price Ravicti On Par With Buphenyl, Capture Share Based On Ravicti's Superior Profile

Hyperion will be in a position to launch Ravicti during H1:13 once Buphenyl and Ammonul are brought in-house, and commercial quantities of Ravicti are manufactured and labeled. Hyperion will promote its UCD franchise via a group of 20 sales and marketing professionals. Hyperion estimates that the UCD market is extremely focused, with 100 physicians writing 80% of Buphenyl scrips, and 30 physicians accounting for 60% of scrips.

Buphenyl is currently priced at a WAC of $2024.64 per 250-pill bottle (each pill is 500mg). In an adult patient that needs 40 pills per day, this would translate into an average price of $118K per patient per year. With the "average" patient on 20 pills per day, the "average" patient is paying $60K per year. While healthy, these prices are quite a bit below that charged for other orphan therapies, which are typically priced in the $200K - $400K/patient/year range.

Upon Ravicti's approval, Hyperion expects to increase the price of Buphenyl so that it and Ravicti are priced on parity. Although Hyperion will only disclose the exact price at the time of Ravicti's launch, we expect it will be consistent with recent orphan disorder launches, and model a price of $200K/patient/year. The Buphenyl price increase will apply specifically to the private-pay portion of the market, as the price increases to the Medicaid portion are limited to the CPI. In fact, Hyperion expects that the Buphenyl price increase will be large enough to put the drug in a "super rebate" situation, in which the additional price increase will be rebated back to Medicaid, essentially making Buphenyl free for Medicaid patients.

Upon Ravicti's approval Hyperion will institute a patient assistance program that will assist patients in obtaining insurance coverage for Ravicti and Buphenyl, and provide financial assistance for anyone who can not afford the drug or copay.

With Ravicti and Buphenyl priced on parity in most of the market, Hyperion expects that a large number of Buphenyl patients will transfer to Ravicti because of Ravicti's superior clinical profile.

Consultants Expect Majority Of Buphenyl Patients To Quickly Transfer To Ravicti When It's Available

We recently checked in with three of our urea cycle disorder physician consultants. These physicians each treat about 30-35 urea cycle disorder patients, with their practices split 50:50 between kids and adults. Aside from the 15-25% of patients in their practices who had received liver transplants, everyone else is on a low protein diet. The more mild patients get to goal on diet alone, but the majority require the chronic use of Buphenyl. There was a relatively wide range in the proportion of patients on Buphenyl in the physicians' practices, ranging from 50% on the low end, to 95% on the high end.

The physicians acknowledge that Buphenyl has revolutionized the treatment of the disease, saving the lives and intelligence of their patients. Nonetheless, the physicians were unanimous that their patients hate Buphenyl. Buphenyl's pill burden is a prominent complaint, as the number of pills is difficult to take each day, and the mass and volume of drug consumed makes the patients uncomfortable. Even more common, all patients get upper gastrointestinal side effects including gastritis, esophagitis, and pain that can be quite severe. The GI effects are so universally reported with Buphenyl that one physician said that they are characteristic of taking Buphenyl. Buphenyl's side effects lead to noncompliance with the regimen, and lower penetration of the market as some patients refuse to take it. Here again, there was some difference in opinion about the degree of noncompliance in the physicians' practices, with the physicians on a spectrum of 50% compliance on the low end, and 95% compliance on the high end. The physicians all think that there are a handful of patients in their practices who probably should be on Buphenyl, but aren't because of its side effects. All of the physicians suggest the number is not large – a relatively small percentage of the patients currently on it.

The physicians are enthusiastic for Ravicti. They characterize its efficacy data as strong. Ravicti has at least demonstrated equivalence with Buphenyl in its ability to control ammonia, and the physicians think the data suggest a strong trend toward superiority. They think the better ammonia control is due in part to better patient compliance, and in part to greater ammonia lowering during the overnight period. They believe that this leads to fewer hyperammonemic crises for patients on Ravicti compared to Buphenyl. A trend toward fewer HA crises has been demonstrated in Ravicti's pooled clinical trial data, and two of our consultants say that they have seen a similar trend in their practices. Nonetheless, Ravicti like Buphenyl is not a cure for UCD, and all patients must still remain adherent to their low protein diets. Our consultants see few deficiencies in the efficacy data so far released by Hyperion, although one is hoping to see a quantification of the rate of hospitalizations on Ravicti in a future data release.

Our consultants think Ravicti's convenience and tolerability are far superior to Buphenyl, and that this is its biggest point of differentiation. While pill burden is a significant complaint of Buphenyl, our consultants say that Ravicti's delivery of a single tablespoon of nearly tasteless and odorless liquid is "fantastic". They say that the volume and taste are virtually "nothing" and that it is very easy to get the patients to stay compliant. Moreover, they say that Ravicti is not associated with any major gastrointestinal side effects. Perhaps there is a little gas or stomach upset if patients take Ravicti on an empty stomach, but these effects are far, far less severe than the GI issues patients encounter on Buphenyl. Our consultants have noticed that their patients are much happier when on Ravicti than when on Buphenyl. Patients have a better appetite, and stay on diet more easily because they do not have the GI side effects. Moreover, because Ravicti is given in a smaller volume, it is easier to take with them as they go about their lives. The combination of the better diet and improved convenience improves their quality of life, and in the words of one consultant, makes it simply "easier to live their life." Consequently, our consultants expect higher compliance with Ravicti than they have seen thus far with Buphenyl.

While Ravicti has numerous advantages over Buphenyl, our consultants could think of no attributes of Buphenyl that are superior to Ravicti.

Our consultants think it likely that Ravicti will be approved on or around its October PDUFA date. Perhaps the two risks to its approval are the rat carcinogenicity data, and the FDA's concerns over the effects of elevated PAA levels in children. Our consultants think the rat carcinogenicity data have little relevance to humans, and are comforted by the long clinical experience with Buphenyl. None are experts in preclinical carcinogenicity models so none think they have great insight into the FDA's opinion of such findings. However, they were largely dismissive of the data and are quite hopeful the application won't be tripped up. The physicians were similarly unconcerned by the elevated PAA levels produced by Ravicti. They don't believe that the cancer literature is particularly relevant to urea cycle disorders, and think that the FDA is being overly cautious. They have never seen any adverse events produced by either Ravicti or Buphenyl that could be tied to high PAA levels, and overall call Ravicti's adverse event profile "very benign". Therefore they do not think concerns over PAA levels should prevent Ravicti's approval. Nonetheless, given the FDA's stated concerns, they do think it is possible that the initial approval could be for children and adults over the age of 6, with a label extension to follow in 2013 once the 12 month safety extension data are available from the Phase III study in younger children. However, given their lack of concern over the PAA issue, and the

significantly improved profile that these physicians think Ravicti has, they would use it off-label in younger children prior to the granting of a formal label.

The physicians expect Ravicti's uptake will be rapid. They expect two-thirds or more of their Buphenyl patients will switch immediately to Ravicti, and that most of the rest will switch over time. They note that most patients who have used Ravicti in clinical trials greatly prefer it to Buphenyl, and they see no reason why this would be different in the real world. In addition, they physicians have a handful of patients who have refused to take Buphenyl, but that these physicians think could tolerate Ravicti. The physicians note this is a relatively small percentage of their total patients, however. Additionally, the physicians say their practices are slowly accumulating urea cycle disorder patients, and they expect all of their new patients to initiate therapy with Ravicti.

Ravicti's Exclusivity To Be Protected By Orphan Drug, Prometheus Puts Label Claim Patents At Risk

Hyperion has licensed Ravicti's composition of matter patents from Brusilow. These patents are issued in the U.S., Canada, and the EU. Although currently set to expire in 2015, Hyperion expects that it will obtain a Hatch-Waxman extension out to 2018. Hyperion also has pending patents in the U.S. and EU that claim methods for adjusting the dose of Ravicti and Buphenyl that, if issued, would expire in 2029. Hyperion also has a second set of label claim patents pending that use fasting ammonia level measurements to determine the dose in UCD patients. If these patents issue they will expire in 2032. Unfortunately, Hyperion thinks the recent Prometheus ruling suggests there is a good amount of risk the 2029 and 2032 patents are either not issued, or do not withstand challenge.

Therefore, it is most likely that Ravicti's exclusivity in urea cycle disorders will be protected by orphan drug exclusivity, which will run for 7 years following its U.S. approval. Ravicti has been granted orphan drug designation for UCD and HE. Because Ravicti contains the same active ingredient as Buphenyl, Ravicti will receive orphan exclusivity for UCD technically only if the FDA concludes Ravicti is safer than Buphenyl, and comparable in terms of efficacy. Nonetheless, Hyperion is very confident that Ravicti will be granted 7 years of exclusivity. Management believes that the Office of Orphan products has determined that Ravicti is safer than Buphenyl because of its lower sodium content, and that this determination was made at the time that the orphan designation was granted. As long as its sodium content remains lower than Buphenyl (which it must) and its label doesn't contain the same warnings against use in patients with heart failure or severe renal insufficiency, Ravicti will be granted the 7 years of exclusivity. Therefore, there would seem to be little risk that Ravicti is not granted the 7 years of exclusivity.

We Expect Ravicti To Achieve $100MM+ In UCD Revenue

Hyperion and the UCD registry estimate that there are 2,000 patients with clinically-evident urea cycle disorders in the U.S. today, with about 30 new cases per year. Of those, about 1,000 are diagnosed, and of the 1,000 patients diagnosed, about 425 are on Buphenyl, and 90 are on Ravicti's extension studies. At an average price of therapy of 55K currently, Buphenyl is generating about $23MM annually for Medicis.

Following Ravicti's approval, we estimate that it will be priced at about $200K/patient/year. Although Buphenyl's WAC will be similar to Ravicti, because the Medicaid portion of the market will be essentially free, its average price per patient will be less, and we estimate $150K.

We assume that Ravicti is launched in mid-2013, and that Hyperion gets rights to Buphenyl at the same time. Our model projects that 67 patients will be on Ravicti during 2013, which we believe is conservative given our consultants expectations for a rapid switch of the market, and the fact that there are 90 patients in Ravicti's extension studies. We project that Hyperion will recognize $32.5MM in Buphenyl revenue in 2013, and $13MM in Ravicti revenue. We expect that overtime Ravicti will capture the vast majority of UCD treated patients, and expand the market modestly by capturing newly diagnosed patients, as well as some that have dropped off Buphenyl because they can not tolerate it. We project that by 2016 there will be 550 patients on Ravicti, and only 33 on Buphenyl, yielding $110MM in Ravicti revenue, and $5MM in Buphenyl revenue.

UCD Revenue Model

	2011A	2012E	2013E	2014E	2015E	2016E
U.S. Urea Cycle Disorder Market						
Chronic Therapy						
Prevalence Of Urea Cycle Disorders In U.S.	2090	2138	2186	2234	2282	2330
Annual Incidence of UCD	160	160	160	160	160	160
Annual Mortality from UCD	112	112	112	112	112	112
Total Patients With Urea Cycle Disorders In The U.S.	2138	2186	2234	2282	2330	2378
% Diagnosed	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*
Number Diagnosed	1045	1069	1093	1117	1141	1165
Buphenyl						
% on Buphenyl	*41%*	*40%*	*40%*	*21%*	*12%*	*3%*
Number of Patients On Buphenyl	425	425	433	233	133	33
Average Cost per Patient per Year ($000)	55	55	75	150	150	150
Buphenyl Revenue ($MM)	**23.4**	**23.4**	**32.5**	**35.0**	**20.0**	**5.0**
Ravicti						
% on Ravicti			*6%*	*27%*	*37%*	*47%*
Number of Patients On Ravicti			67	300	425	550
Average Cost per Patient per Year ($000)			200	200	200	200
Ravicti Revenue			**$13.3**	**$60.0**	**$85.0**	**$110.0**
Y/Y Growth				*350%*	*42%*	*29%*

Source: Cowen and Company

Hyperion Is Undervalued Based On UCD Alone

We have built a discounted cash flow analysis of Hyperion UCD business. Our analysis incorporates the Buphenyl and Ravicti estimates discussed in the preceding section, as well as estimates for Ammonul sales of $8-10MM annually. We assume that Ravicti's exclusivity is protected only by Orphan Drug exclusivity, and that competition comes against it beginning in 2020. However, we assume that there is only limited competition given Ravicti's revenue, and that Hyperion's services and reimbursement support slow the rate of decline of patients off of Ravicti. We project that the franchise will decline by 20% per year following 2020. Using these assumptions, a 10% discount rate, and a -10% terminal growth rate, our analysis suggests Hyperion is significantly undervalued.

Hyperion DCF

Financial Year End	12/31/2011
Valuation Date	8/15/2012
Discount Rate	**10.0%**
Terminal Growth Rate	**-10.0%**

Hyperion: DCF Valuation
Wednesday, August 15, 2012

$MM	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026
Ravicti Sales	**0**	**13**	**60**	**85**	**110**	**132**	**145**	**152**	**122**	**98**	**78**	**62**	**50**	**40**	**32**
Growth (%)			*350%*	*42%*	*29%*	*20%*	*10%*	*5%*	*-20%*	*-20%*	*-20%*	*-20%*	*-20%*	*-20%*	*-20%*
Buphenyl	**0**	**33**	**35**	**20**	**5**	**4**	**4**	**3**	**3**	**2**	**2**	**2**	**1**	**1**	**1**
Growth (%)			*8%*	*-43%*	*-75%*	*-15%*	*-15%*	*-15%*	*-15%*	*-15%*	*-15%*	*-15%*	*-15%*	*-15%*	*-15%*
Ammonul	**0**	**4**	**9**	**9**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Growth (%)			*113%*	*6%*	*6%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
License and Other	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Growth (%)															
Total Revenues	**0**	**50**	**104**	**114**	**125**	**146**	**158**	**165**	**134**	**109**	**89**	**74**	**61**	**51**	**42**
Growth (%)			*108%*	*10%*	*9%*	*17%*	*9%*	*4%*	*-19%*	*-18%*	*-18%*	*-18%*	*-17%*	*-17%*	*-16%*
COGS	**0**	**3**	**9**	**10**	**12**	**14**	**16**	**16**	**13**	**11**	**9**	**7**	**6**	**5**	**4**
COGS as a % of sales		*25%*	*14%*	*12%*	*11%*	*11%*	*11%*	*11%*	*11%*	*11%*	*11%*	*12%*	*12%*	*13%*	*13%*
R&D	**18**	**19**	**22**	**24**	**25**	**22**	**21**	**18**	**13**	**11**	**9**	**7**	**6**	**5**	**4**
R&D as a % of Revenues		*39%*	*21%*	*21%*	*20%*	*15%*	*13%*	*11%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*
SG&A	**11**	**22**	**25**	**28**	**28**	**29**	**28**	**26**	**16**	**13**	**11**	**9**	**7**	**6**	**5**
SG&A as a % of Revenues		*43%*	*24%*	*24%*	*22%*	*20%*	*18%*	*16%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*	*12%*
Operating Income	**-29**	**-31**	**4**	**23**	**45**	**67**	**80**	**92**	**79**	**63**	**50**	**39**	**31**	**24**	**18**
Tax	**0**	**0**	**0**	**3**	**14**	**20**	**24**	**27**	**24**	**19**	**15**	**12**	**9**	**7**	**6**
Tax rate	*0%*	*0%*	*6%*	*15%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
NOL/ Tax Assets Utilized															
Tax rate															
Taxes Paid	**0**	**0**	**0**	**3**	**14**	**20**	**24**	**27**	**24**	**19**	**15**	**12**	**9**	**7**	**6**
Approx Free Cash Flow	**(29)**	**(31)**	**4**	**20**	**32**	**47**	**56**	**64**	**55**	**44**	**35**	**27**	**21**	**17**	**13**
Years	0.37	1.37	2.37	3.37	4.37	5.37	6.37	7.37	8.37	9.37	10.37	11.37	12.37	13.37	14.37
Discount Factor	0.96	0.88	0.80	0.73	0.66	0.60	0.54	0.50	0.45	0.41	0.37	0.34	0.31	0.28	0.25
NPV of Cash flows	**(28)**	**(27)**	**3**	**14**	**21**	**28**	**31**	**32**	**25**	**18**	**13**	**9**	**7**	**5**	**3**

Terminal Value Calculation

Final year FCF	13
Perpetual Growth Rate	-10.0%
Terminal Value	**58**
Discount Factor	0.25
Present Value of Terminal Value	**15**
Present Value of Cash Flows	**167**
Enterprise Value	**182**
Add: Net cash	47
Market Value	**229**
Fully Diluted Shares Outstanding	16.6
Value per Fully Diluted Share	**$13.81**

Source: Cowen and Company

Hepatic Encephalopathy Represents A Possible Growth Opportunity

Hepatic Encephalopathy (HE) refers to a condition of worsening brain function resulting from a buildup of toxins in the blood due to a failure of the liver to remove those toxins. HE can potentially occur secondary to a variety of disruptions in normal liver function, but etiology of chronic HE most commonly involves cirrhosis due to alcohol abuse or hepatitis infection. The disease is quite prevalent; according to the U.S. Department of Health and Human Services' Healthcare Utilization Project (HCUP), 340,000 U.S. patients may suffer from overt episodic HE. The outward presentation of HE can include confusion, changes in mood or sleeping patterns, paroxysmal motor movements, coma and death. Though the exact toxic species responsible for neurologic symptoms in HE are unknown and likely multifactorial, consultants indicate that there is broad acceptance in the medical community that ammonia is a key player, in part because of the similarity in presentation between HE and UCD.

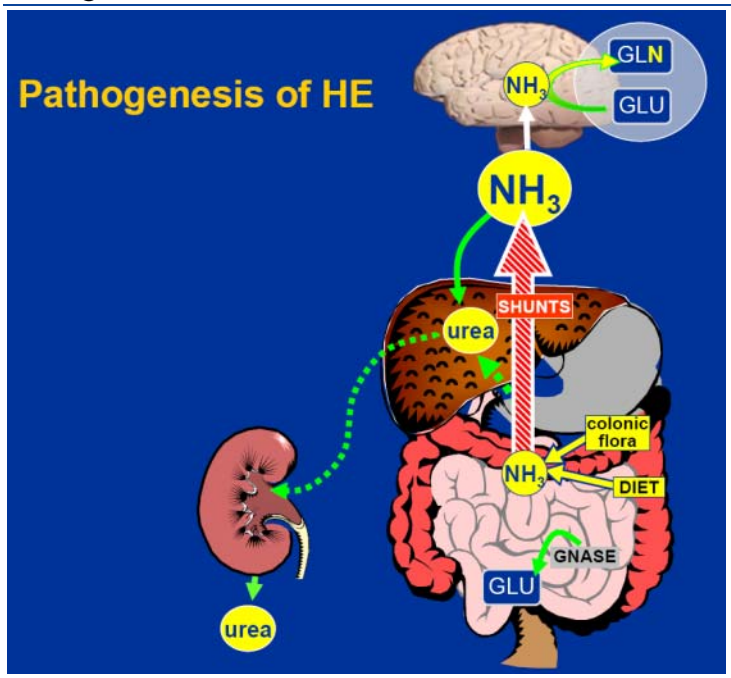
Patients with chronic HE may experience transient episodes of worsening neurologic symptoms, or "HE events," which frequently require hospitalization. Approved agents for reducing the risk of HE events are thought to work by nonspecifically impairing the metabolic production of ammonia by intestinal bacteria, but these agents have limitations. Hyperion is hopeful that Ravicti's systemic, ammonia-selective mechanism of action may prove useful in preventing HE events, with potentially superior and/or complementary efficacy vs. available agents. Hyperion has successfully completed Phase I and II testing for Ravicti in HE, and plans to move into Phase III, pending an end of Phase II meeting with the FDA in Q4:12. We believe Ravicti could yield $300MM+ in sales in HE, if successfully developed.

HE: Disease Pathology And Prevalence

HE is a complication of advanced liver disease characterized by neurological dysfunction that may manifest as disturbances in cognitive function, personality/behavior, neuromuscular function, and consciousness. Clinical diagnosis and grading of severity is based on two main measures: (1) impaired mental status (typically measured by the Conn Score, a.k.a. West Haven score) and (2) impaired neuromotor function (e.g., asterixis, tremor of the outstretched hand). Severity of symptoms can range from mild disturbances to coma and death.

HE is thought to result from the inability of a dysfunctional liver remove toxic metabolites from the blood, or from bypass of the hepatic portal circulation entirely via shunting vessels passing blood from the intestine directly to systemic circulation. (Both of these are consequences of cirrhosis, which consultants say is responsible for 95% of HE). The principal source of such toxic metabolites is believed to be the intestine, resulting from both the metabolic activities of commensal gut bacteria, as well as the host's own metabolic enzymes. Ammonia is suspected as the major species at fault, in part because blood ammonia is elevated in up to 90% of HE patients, and reductions in ammonia level correlate with improved HE grade. Moreover, astrocytes are the only cells in the brain capable of metabolizing ammonia (by conversion of glutamate to glutamine), and these are found to be swollen in HE patients. However, correlation with blood ammonia level and HE severity is imperfect, and other metabolites have also been implicated.

Pathogenesis of HE

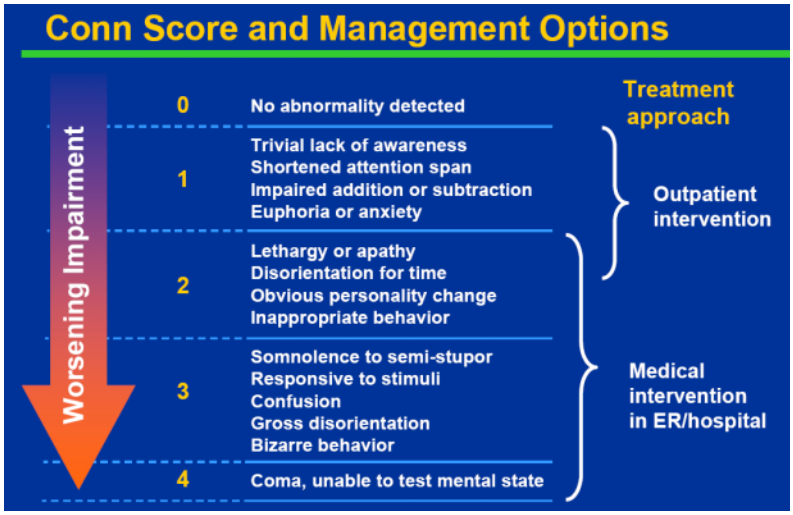


Source: Salix 2010 FDA AdCom Slides

HE is most commonly seen secondary to cirrhosis of the liver, a widespread problem accounting for about 35,000 U.S. deaths annually (9th leading cause of death). The incidence of cirrhosis is increasing as a consequence of chronic HCV infection, and up to 1 million Americans are now thought to be affected. According to consultants, clinically recognizable HE occurs in 30-50% of cirrhosis patients. HE can also occur secondary to portal systemic bypass in the absence of intrinsic liver disease, affecting 10-50% of such patients, but this is a relatively small source of HE patients. According to consultants, the prevalence of HE is uncertain, though they agree that it is increasing with time due to chronic HCV infection. Hyperion estimates that clinically recognizable, overt, episodic HE affects 140,000 Americans (based on triangulation of NHANES cirrhosis data, a Medicare patient database, and private pay databases). Meanwhile, Salix has cited an estimate of 340,000 U.S. HE patients based on the HCUP database. U.S. government records show 48,000 hospitalizations for hepatic coma annually.

Many HE patients manifest "episodic" disease, with periods of relative normalcy punctuated by bounds of worsened symptoms, though some patients exhibit "persistent" disease, with chronic, waxing and waning symptoms. HE episode severity can be graded by the Conn/West Haven score, ranging from 0 (no symptoms) or 1 (manageable outpatient) to 2, 3, or 4 (increasingly severe, usually requiring hospitalization).

Conn Grading Of The Severity Of HE Episodes



Source: Salix 2010 FDA AdCom Slides

Current Treatments Have Drawbacks

There are currently three FDA approved treatments for HE: Salix's rifaximin (an antibiotic approved for this indication in 2010), and generic lactulose (non-absorbable sugar) and generic neomycin (an antibiotic). Two other antibiotics, metronidazole and vancomycin, are sometimes used off-label. All of these therapies essentially rely on nonspecific interference with the metabolic activity and/or survival of intestinal flora in order to reduce the productions of ammonia and other toxins, and all have their drawbacks.

Approved Therapies For HE

	Lactulose	Neomycin	Rifaximin
Mechanism	Traps ammonia and inhibits bacterial production Bowel flushing	Kills bacteria, preventing ammonia production	Kills bacteria, preventing ammonia production
Limitations	Relies on self-titration Can cause severe diarrhea Can cause deydration, electrolyte imbalance GI side effects Poor adherence Questionable/variable efficacy	Potentially nephrotoxic, ototoxic Questionable efficacy Only approved for acute use	Incomplete efficacy Not ammonia-selective

Source: Salix 2010 FDA AdCom Slides, Cowen and Company

The older therapies include lactulose (FDA approved in 1976 for prevention and treatment of portal-systemic encephalopathy) and the antibiotics neomycin (FDA approved in 1970 as an adjunctive therapy for treatment of hepatic coma), metronidazole, and vancomycin. Lactulose is a disaccharide that cannot be absorbed from the intestine. It is fermented by intestinal bacteria, which limits ammonia production and also results in a lowered bowel pH. The lower pH drives conversion of ammonia to non-absorbable ammonium, and also promotes flushing (diarrhea) which expels accumulated ammonia and the bacteria responsible. Patients must be dose titrated, with the goal of reaching 3-5 soft stools per day. This diarrhea is suboptimal for the patient's quality of life, is associated with GI discomfort, leads to poor adherence, and can also cause dehydration and even exacerbation of HE. Moreover, meta-analysis of numerous lactulose trials by the Cochrane group have not revealed conclusive evidence that lactulose is even effective as a prophylactic in

episodic HE. Nevertheless, lactulose has been the first-line standard of care in the condition.

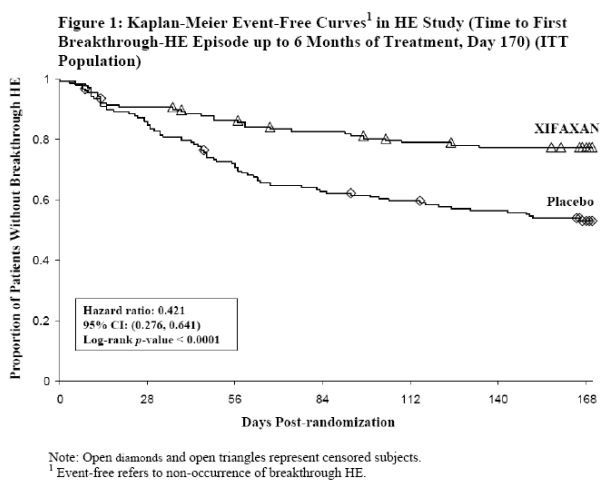
The antibiotics neomycin and metronizadole have been used as second-line treatments for HE, with the rationale being that killing the intestinal bacteria could similarly reduce ammonia production, while the drugs' relatively poor systemic absorption could render them safe. However, it was later found that neomycin is absorbed sufficiently to potentially cause ototoxicity and nephrotoxicity with long-term use, and metronizadole can cause peripheral neuropathy and GI upset. Furthermore, the Cochrane meta-analysis showed no superiority of these antibiotics over lactulose in efficacy. Consultants say neomycin, metronizadole, and vancomycin are not commonly used in chronic HE treatment today, largely being limited to acute treatment of breakthrough attacks (and swiftly being supplanted by rifaximin, see below).

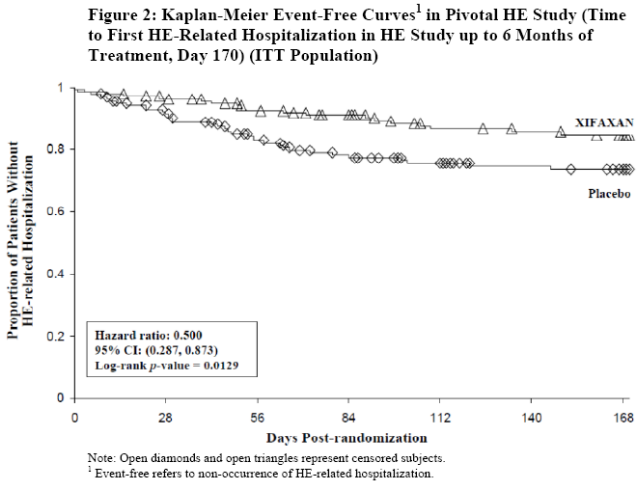
Salix's Rifaximin The Newest Approval In HE

Salix's rifaximin (XIFAXAN) is a poorly-absorbed antibiotic that had been used off-label for some years in the treatment of HE, supported by academic studies showing efficacy. After Salix conducted a pivotal Phase III trial, rifaximin received an FDA label expansion for the reduction in risk of recurrence of HE episodes in 2010 (the drug was first approved for traveler's diarrhea in 2004). Like the other antibiotics, rifaximin is thought to work locally in the intestine to prevent bacterial production of ammonia. As the only drug to win approval in this indication in the modern era, however, rifaximin has easily the most robust clinical trial evidence showing efficacy and safety. Rifaximin's approval in HE was based on a single double-blind Phase III trial enrolling 299 patients. The patients had to be in remission (Conn score of 0 or 1) at study entry, and they had to have had at least two HE episodes in the 6 months prior to study entry. Patients were randomized to 550 mg rifaximin BID or placebo, on top of background therapy (91% were receiving concomitant lactulose), and were followed for six months. The primary endpoint was time to first HE breakthrough, defined as a Conn score of 2 or greater. Alternately, if the baseline Conn score was 0, breakthrough could also be defined as a Conn score of 1 and an asterixis score that increased by 1. Time to HE-related hospitalization was a key secondary endpoint.

Rifaximin reduced the risk of HE breakthrough by 58% over the 6-month treatment period: 31/140 rifaximin subjects (22%) experienced breakthrough attack, vs. 73/159 control patients (46%). HE-related hospitalizations were reported for 19/140 rifaximin patients (14%) vs. 36/159 patients (23%) in the control group, a 50% reduction in risk. Rifaximin also improved scores on quality of life (as measured by the CLDQ).

Rifaximin's Phase III Efficacy Data





Source: FDA label

Rifaximin's safety experience supporting the HE indication included 348 patients, with 265 exposed for 6 months and 202 exposed for more than one year. (The overall safety database, from trials in all indications, was over 4,000 patients). In the HE patients, the drug was well-tolerated, with AEs and SAEs balanced with placebo. Among specific AEs, there was a slight numerical imbalance in peripheral edema and dizziness, but little else of note. No convincing signal of hepatotoxicity, nephrotoxicity, or increased infection risk was observed.

Consultants Say Lactulose Remains Standard Of Care, But Rifaximin Gaining Fast

Consultants indicate that patients presenting with acute HE attacks tend to receive lactulose, electrolytes, and antibiotics while being evaluated for a precipitating cause (such as dehydration, GI bleed, etc). Usually, such a cause can be identified and remedied, and the patient then usually recovers. However, our consultants estimate that 80-90%+ of HE patients should then be receiving chronic, prophylactic treatment to reduce risk of further attacks. Our consultants say that most patients are treated with lactulose, though hepatologists believe rifaximin provides an additive benefit and are increasingly putting their patients on that drug as well. Consultants say the major barrier to rifaximin use is cost; prior authorization paperwork and co-pay cost to the patient can be prohibitive. As a result, perhaps only 10-15% of their more indigent patients may be on treatment with rifaximin today, though the percentage is higher than that among those with high quality insurance.

Consultants say that lactulose leaves much to be desired in terms of tolerability, with poor compliance due to unpleasant taste and GI side effects. They say rifaximin is more tolerable, but its major drawbacks are (1) cost and (2) incomplete efficacy (approximately 20% of patients continue to have breakthrough attacks on rifaximin).

Ravicti's Clinical Development In HE

While rifaximin is becoming the new standard of care in HE event prophylaxis, approximately 20% of treated patients experienced breakthrough attacks during the 6 months of rifaximin's pivotal trial. Therefore, Hyperion believes that there remains

unmet need in the prevention of HE attacks. The company is therefore conducting clinical development of Ravicti in HE as a possible market expansion opportunity. Hyperion's rationale for developing Ravicti in this disease is that, unlike available agents, Ravicti is: (1) ammonia-selective and (2) systemically acting. Therefore, there is the possibility that Ravicti may offer superior efficacy to available agents, either as a monotherapy or perhaps in combination, through its complementary mechanism of action. While Buphenyl would seem in principle to be an appropriate treatment option for HE, in fact it is not, due to the FDA warning against use in patients with high sodium and/or edema, common issues in HE. Hyperion has completed a successful Phase II trial of Ravicti in prophylaxis of episodic HE and plans to hold an end of Phase II meeting with the FDA in Q4:12 to discuss Phase III design.

Initial Phase I testing (by Ucyclyd) characterized Ravicti's safety in 24 adults with cirrhosis relative to 8 healthy patients. There was no material difference between the groups. The trial also showed that, though cirrhotic patients with severely impaired liver function may metabolize Ravicti more slowly than healthy adults, the cirrhotics were able to metabolize the drug efficiently enough to promote ammonia removal.

The Phase II trial was composed of an initial open label dose escalation stage, followed by a double-blinded treatment stage. In the dose escalation stage, 15 patients with cirrhosis and HE were treated with 6mL or 9mL Ravicti BID. The two dosages were approximately equal in effectiveness at lowering blood ammonia (approximate 35% decrease in mean fasting level), while the 6mL dose was better tolerated. Therefore the 6mL dose was advanced into the Phase II treatment stage.

The double-blinded Phase II treatment stage was designed using rifaximin's pivotal trial as a model. Hyperion's Phase II trial enrolled 178 HE patients and randomized them to Ravicti (n = 90) or placebo (n = 88) on top of standard of care (lactulose and/or rifaximin). As with the rifaximin Phase III, patients had to have had at least two HE events in the 6 months prior to enrollment despite continuous standard of care. The primary endpoint was the proportion of patients with one or more HE events during four months of treatment (similar to rifaximin's primary endpoint of time to first HE event during 6 months of treatment). "HE event" in this trial was defined the same as in rifaximin's pivotal trial (see above). A notable design difference between the Hyperion and Salix trials was that the Salix trial required exit of a patient after experiencing an HE event, while Hyperion's trial permitted patients to stay on treatment after an HE event, and allowed modification of standard of care treatment (including introduction of rifaximin to patient who had not previously received it). Prespecified secondary endpoints included total HE events, time to first HE event, and change from baseline in Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) score (included to assess impact on so-called "minimal HE"). Additional secondary endpoints included hospitalizations due to HE and proportions of subjects with one or more symptomatic days.

Eighty-eight patients were enrolled at 28 sites in the U.S. and 90 patients were enrolled at 16 sites in Russia and Ukraine. In May 2012, Hyperion reported that the trial succeeded on its primary endpoint: Ravicti significantly reduced the proportion of patients experiencing at least one HE event, with 19 of 90 Ravicti patients (21%) experiencing an event vs. 32 of 88 (36%) of placebo patients (42% reduction, p = 0.02). Ravicti also significantly reduced the total HE events on study and the number of subjects with a symptomatic day, and produced a numerical reduction in the total

HE-related hospitalizations. (The RBANS endpoint relating to minimal HE was not met.)

Ravicti's Overall Phase II Efficacy In HE

	Ravicti N=90	Placebo N=88	% Reduction	p value
Primary Efficacy Endpoint: Patients with at least one HE event # of subjects and %	19 21.1%	32 36.4%	42%	0.021
Total HE Events	35	57	37%	0.035
Subjects with a Symptomatic Day*	13	27	52%	0.015
Total HE Hospitalizations	13	25	48%	0.064

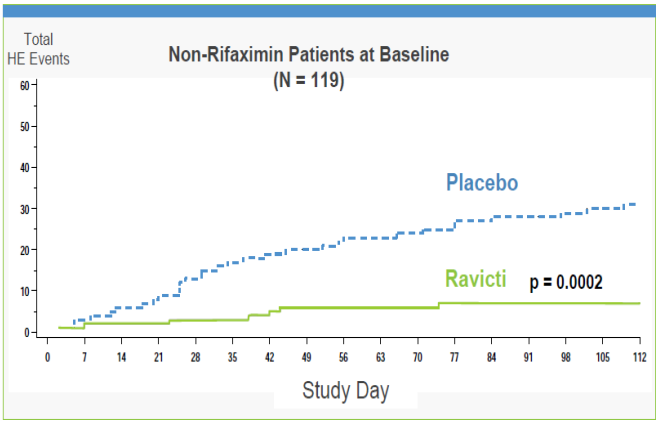
* Corresponds generally to West Haven ≥2

Source: Hyperion Therapeutics

In order to draw a reasonably apples-to-apples comparison between Ravicti's Phase II data and rifaximin's pivotal data in HE, Hyperion conducted a subset analysis of the patients in the Ravicti trial who were not being treated with rifaximin at baseline. These trial populations are thus rendered fairly comparable, with the usual caveats about cross-trial comparisons, except that (1) rifaximin's trial was 6 months in duration to Hyperion's 4 months; (2) rifaximin had n = 299 vs Hyperion's n=112 in this subset; and (3) patients were dropped from the trial in Salix's study after their first HE event, but could be kept on study (and receive different background therapy) post the first HE event in Hyperion's study. Subject to these cautions, Ravicti's data appear at least as good as rifaximin's on this background of care: Ravicti showed a significant reduction in proportion of patients with any HE event (6 of 60 patients (10%) on Ravicti vs. 19 of 59 patients on placebo (32%), p =0.003), as compared to 22.1% of rifaximin patients vs. 45.9% of placebo patients (p < 0.001) in rifaximin's pivotal trial. Similarly robust data were observed in this patient subset on proportion of patients with severe HE events (Conn score of 2 or greater) and total HE events on study, though interpretation of these metrics is somewhat difficult, given that patients could change background therapy and may or may not have dropped out after the first HE event.

Ravicti's Phase II Subset Analysis in HE

	Rifaximin Pivotal	Hyperion Phase 2 "Rifaximin Analysis"
Duration	168 days	112 days
No rifaximin at baseline*	N= 299 (all)	N=119
Primary Endpoint (% of Patients with Any HE Event)		
Placebo	45.9%	32.2%
Active	22.1%	10.0%
p-value	<0.0001	0.003
Reduction in risk of HE events	58%	71%
More Severe Cases (% of HE Events ≥ WH 2)		
Placebo	35.8%	28%
Active	20%	5%
p-value	0.002	0.002
Reduction in risk of HE events	NP**	82%



Source: Hyperion Therapeutics

Turning to the complementary subset analysis, those patients who were receiving rifaximin at study baseline, the Phase II data are somewhat murkier as to whether

Ravicti can offer an additional efficacy benefit on top of background rifaximin. Ravicti patients who were on rifaximin at baseline (n = 30), 43.3% experienced at least one HE event, similar to the 44.8% of placebo patients on rifaximin at baseline (n = 29). Ravicti patients in this group did experience numerically fewer HE hospitalizations (11 for Ravicti vs. 20 for placebo), but not fewer patients with HE events (13 vs. 13). Hyperion has suggested that the requirement that this subset of patients have failed rifaximin within the pre-trial months may have selected unusually difficult patients, which would be consistent with the rather high HE event rate on both arms.

A separate analysis was conducted on a slightly broader subgroup of patients, those who received rifaximin at any time on study (including patients who were on rifaximin at baseline and those who began on placebo but received rifaximin after their first HE event). There were 31 such Ravicti patients and 38 such placebo patients. In this subgroup, numerically fewer patients experienced HE events on Ravicti vs. placebo (13 vs. 22) and numerically fewer total HE events occurred on Ravicti vs. placebo (28 vs. 42). However, its unclear how strong evidence this provides for a benefit of Ravicti over rifaximin. The differences between groups may have been largely driven by HE events that occurred when the placebo patients were on lactulose alone, before rifaximin was added to their therapy.

The safety results in Ravicti's Phase II trial were as follows. The adverse event rate was similar between the drug and placebo arms. The SAE rate was higher on the Ravicti arm (20 SAEs, 1 scored as possibly related to treatment, vs 12 SAEs on placebo, 4 scored as possibly related to treatment). There were three deaths on the trial, two on Ravicti and one on placebo, which were all scored as unrelated to treatment. Hyperion has disclosed a randomization imbalance of severely ill patients to the Ravicti arm (21 Child-Pugh C patients on Ravicti vs. 8 on placebo), which could account for the imbalance of SAEs and deaths.

Full data from the Phase II trial are anticipated at the AASLD meeting in November 2012. Hepatologist consultants will focus on details of enrolled patient subgroup demographics (i.e. geographic split, number of events at entry), details of adverse event differences between subgroups, and whether there is any documented correlation between ammonia levels and clinical symptoms.

Consultants Expect Ravicti To Find A Path To Market

Consultants believe Ravicti's efficacy data on the background of lactulose alone convincingly show that the drug is active at lowering the risk of HE attacks, and looks at least as effective as rifaximin. They also see no evidence of major red flags on safety. They therefore think Ravicti has a good chance of being approved for this indication, assuming Hyperion pursues development.

However, they say the limited evidence thus far for Ravicti's potentially additive efficacy on top of rifaximin may make it challenging to find the right trial design and patient population for a pivotal study. Hyperion may conduct a Phase III trial in which patients on rifaximin at study entry may not need to have failed rifaximin, which could reduce selection of more difficult patients. However our consultants point out that patients really need to be having breakthroughs on baseline treatment, or it would be difficult to define an efficacy endpoint. Consultants have suggested that a Phase III trial simply pitting Ravicti against lactulose could be sufficient to support approval (although we think this would perhaps not optimize commercial uptake). Alternative trial designs they suggest could be (1) conducting a

trial designed to replace lactulose in the typical lactulose/rifaximin regimen; (2) conducting a trial in lactulose-refractory patients; (3) a head to head trial vs. rifaximin. We await further clarity on Ravicti's pivotal trial design following the end of Phase II meeting.

Ravicti's Potential Market Opportunity In HE

HE is a large market opportunity. According to the Department of Health and Human Services HCUP database, there may be 340,000 Americans affected by episodic HE. The approval of Salix's rifaximin in the indication has been a testament to the unmet need: following the May 2010 launch, we estimate rifaximin sales in HE alone of about $100MM in 2010, $300MM in 2011, and nearly $200MM in H1:12, based on IMS data. With rifaximin currently priced at about $15,000 per patient per year, Salix has suggested that it may ultimately achieve $1B+ in sales in HE alone. Although rifaximin's orphan drug protection will expire in HE in 2017, polymorph patents may protect the franchise. Moreover, the FDA has issued draft guidance requiring clinical trials to support any ANDA for rifaximin in traveler's diarrhea, suggesting rifaximin will remain incumbent in the HE market for the foreseeable future.

Ravicti's Phase II data in HE appear to give a convincing signal of efficacy, at least in patients not on treatment with rifaximin at baseline. While the Phase III design remains to be established, Hyperion envisions running a trial of Ravicti on top of standard of care (which would include rifaximin in at least some patients). We believe Ravicti may have an opportunity as a second-line HE treatment. Furthermore, the full Phase III dataset may yield meaningful differences in product profile (for example, superior efficacy, or perhaps reduced *C. difficile* infection risk vs. antibiotic approaches). A clear picture of Ravicti's potential must await Phase III data. Nonetheless, as an illustration of Ravicti's potential in HE, our model below suggests that even primarily second-line use, with very modest penetration into the first line, could support $300MM+ in U.S. sales alone.

U.S. Hepatic Encephalopathy Revenue Model

	2010A	2011A	2012E	2013E	2014E	2015E	2016E	2017E	2018E	2019E	2020E
U.S. Hepatic Encepthalopathy Market											
Chronic Therapy											
Prevalence of Overt Episodic HE in the U.S.	340000	340000	340000	340000	340000	340000	340000	340000	340000	340000	340000
Rifaximin											
% on Rifaximin	*4%*	*7%*	*9%*	*11%*	*11%*	*11%*	*11%*	*11%*	*11%*	*11%*	*10%*
Number of Patients On Rifaximin (000)	12.28	24.0	31.1	35.7	38.1	38.9	38.9	38.5	37.8	36.8	35.5
Net Price per Patient per Year ($000)	$12.1	$12.7	$13.3	$14.0	$14.7	$15.4	$16.2	$17.0	$17.9	$18.8	$19.7
Rifaximin Revenue In HE ($MM)	**104.0**	**305.0**	**415.0**	**500.0**	**560.0**	**600.0**	**630.0**	**655.0**	**675.0**	**690.0**	**700.0**
Y/Y Growth		*193%*	*36%*	*20%*	*12%*	*7%*	*5%*	*4%*	*3%*	*2%*	*1%*
Ravicti											
% rifaximin patients failing treatment								*25%*	*25%*	*25%*	*25%*
Number Rifaximin Patients Failing Treatment (000)								9.6	9.4	9.2	8.9
% rifaximin failures on Ravicti								*8%*	*25%*	*40%*	*48%*
Number Of Rifaximin-Failure Patients On Ravicti (000)								0.7	2.4	3.7	4.3
% naïve patients starting Ravicti								*1%*	*2%*	*2%*	*3%*
Number Of Naïve Patients On Ravicti (000)								3.1	6.0	7.8	8.9
Total Patients On Ravicti (000)								3.8	8.4	11.5	13.2
Net Price per Patient per Year ($000)								$17.0	$17.9	$18.8	$19.7
Ravicti Revenue In HE ($MM)								**65.0**	**150.0**	**215.0**	**260.0**
Y/Y Growth									*131%*	*43%*	*21%*

Source: Cowen and Company

Ravicti Has Orphan Designation In HE

Ravicti has received U.S. orphan drug designation for the intermittent or chronic treatment of patients with cirrhosis and any grade HE. Thus, approval in this indication should prevent any generic approvals for the same indication for at least seven years. One risk to Ravicti's market exclusivity in HE, however, is the market exclusivity position of Ravicti in UCD. With the composition of matter patent expiring in 2018, and orphan drug exclusivity for UCD (if granted) expiring in approximately 2020, there is risk that a generic could be approved for UCD and pose off-label competition in HE, unless Ravicti's exclusivity in UCD can be extended. This risk is mitigated, however, by the strategic difficulty any generic company would likely perceive in developing a generic for the UCD indication and then attempting to penetrate HE off–label, with no promotion for that indication being legally permissible.

Positives

1. With a purchase option on two approved products, Hyperion is very likely to begin generating revenue in 2013.
2. Ravicti has successfully completed Phase III trials in UCD, so its clinical development risk in UCD is low.
3. Our DCF analysis suggests Hyperion is substantially undervalued for Ravicti's potential in UCD.
4. Ravicti has produced promising Phase II data in a second indication, HE.

Negatives

1. The length of exclusivity for Ravicti in UCD is unclear, and may be limited to 7 years of orphan drug exclusivity in the United States.
2. UCD is an ultra-orphan condition, and so there is a limited number of patients addressable by Ravicti with the condition in the U.S.
3. While Ravicti's early HE data is interesting, much clinical development and commercial risk remain.
4. Should Hyperion pursue Ravicti in HE, the company would likely need to finance again.

Addendum

STOCKS MENTIONED IN IMPORTANT DISCLOSURES

Ticker	Company Name
HPTX	Hyperion Therapeutics

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Cowen and Company, LLC. New York (646) 562-1000 **Boston** (617) 946-3700 **San Francisco** (415) 646-7200 **Chicago** (312) 577-2240 **Cleveland** (440) 331-3531 **Atlanta** (866) 544-7009 **London (affiliate)** 44-207-071-7500 **Geneva (affiliate)** 41-22-707-6900

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