

PAH Treatments

COMPANIES: ATLN VX, PFE, UTHR



UTHR'S
TYVASO &
ADCIRCA

Rapid Launch Projected For UTHR's New PAH Drugs

Spurred by more convenient dosing that could improve patient compliance, usage of United Therapeutics' Tyvaso and Adcirca is expected to ramp strongly through mid-2010, largely at the expense of Actelion's Ventavis and Pfizer's Revatio.



ATLN VX'S
VENTAVIS

- OTR Global's read on UTHR's Tyvaso and Adcirca is positive; the read on ATLN VX's Ventavis is negative
- Early familiarity with Tyvaso and Adcirca very high; all but 1 source expect to prescribe both by year-end
- Tyvaso and Adcirca use expected to ramp sharply from 3 and 35 patients currently to 180 and 311 by year-end, respectively
- ATLN VX's Ventavis scrips expected to drop from 191 in September to 132 by year-end; 22 of 24 sources do not expect Tyvaso to cannibalize Remodulin
- Areas to Watch: Cumbersome device used to administer Tyvaso could prove a hindrance for some PAH patients; potential headache side effects associated with Adcirca

EXECUTIVE SUMMARY

Although **United Therapeutics Inc.**'s new treatments for pulmonary arterial hypertension (PAH), Tyvaso and Adcirca, only recently received FDA approval, sources are very familiar with them and all but one expect to prescribe both drugs by year-end. Sources expect Tyvaso and Adcirca prescriptions volumes to increase rapidly to 5%–7% and 9%–11% of their PAH patients by year-end, respectively. Sources also praised both drugs' convenient dosing schedules, with many saying treatment compliance will improve as a result. **Actelion Pharmaceutical Ltd.**'s inhaled drug Ventavis, which has a much less attractive dosing regimen than Tyvaso, is expected to lose share, with PAH patient penetration falling 30%–32% by year-end. However, uncertain reimbursement terms and concerns about Tyvaso's cumbersome inhalation system could prove stumbling blocks. Meanwhile, **Pfizer Inc.**'s Revatio is likely to be shunned in favor of Adcirca for new patient starts and switches because Adcirca requires only once-daily dosing.

KEY DATA

Rapid Ramp in Tyvaso, Adcirca Prescribing through Mid-2010 (number of sources)

	CURRENT		DECEMBER 2009		MID-2010	
	TYVASO	ADCIRCA	TYVASO	ADCIRCA	TYVASO	ADCIRCA
101 or more	-	-	-	-	-	1
91–100	-	-	-	-	2	1
61–70	-	-	-	-	-	1
51–60	-	-	-	-	1	3
41–50	-	-	-	1	-	-
31–40	-	-	1	2	-	1
21–30	-	-	2	4	2	-
11–20	-	-	1	-	1	5
1–10	1	8	18	16	16	11
0	22	15	1	-	1	-
Total	3	35	180	311	419	958
PAH patient penetration	Less than 1%	0%–2%	5%–7%	9%–11%	12%–14%	29%–31%

SOURCES & BACKGROUND

25 U.S. PAH treatment specialists treating more than 3,300 PAH patients (1 source not included in the tally)

INTERVIEWS Late August through mid-September

AVERAGES Weighted according to the number of patients treated by each source

BACKGROUND PAH is a rare blood vessel disorder of the lung in which the pressure in the pulmonary artery rises above normal levels and may become life threatening. United Therapeutics' drug Tyvaso (treprostonil) is an inhaled formulation of the company's existing PAH drug Remodulin, which belongs to a class of drug known as prostacyclins. Remodulin is typically indicated for severe PAH, while Tyvaso will be given to patients with moderate-to-severe PAH. On July 31, the FDA approved Tyvaso for PAH patients in WHO group 1. The only other inhaled PAH drug on the market is Actelion's Ventavis (iloprost), which is indicated for moderate-to-severe PAH Adcirca (tadalafil) and received FDA approval on May 26. It is the only once-daily phosphodiesterase-5 (PDE-5) inhibitor for PAH WHO Group I. The drug, taken as 2 tablets once daily, is designed to have the same effect as three doses of Pfizer's PDE-5 inhibitor, Revatio (sildenafil). Both Adcirca and Revatio are indicated for mild PAH. Both may be prescribed as standalone treatments, but as a patient's disease progresses, either may be given in addition to other PAH drugs.

"Tyvaso is great. It has a more convenient dosing frequency and takes less time to administer [than Ventavis]."

PAH treatment specialist at an East Coast center

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PAH Treatments

Marketed Name	GENERIC	PATH OF ADMINISTRATION	MARKETED BY	PAH PATIENT TYPE	APPROXIMATE ANNUAL COST
Adcirca	tadalafil	Oral	UTHR	Mild	\$10K
Revatio	sildenafil	Oral	PFE	Mild	\$13K
Tracleer	Bosentan	Oral	ATLN	Moderate	\$40 - \$50K
Letaris	ambrisentan	Oral	GILD	Moderate	\$45 - \$60K
Tyvaso	treprostinil sodium	Inhaled	UTHR	Mod/Severe	\$176K
Ventavis	iloprost	Inhaled	ATLN	Mod/Severe	\$160K - \$245K
Remodulin	treprostinil sodium	IV and SC	UTHR	Severe	\$120 - \$140K

Familiarity with New PAH Treatments High

Despite being recently approved, most of OTR Global's PAH sources are very familiar with United Therapeutics' new PAH drugs. Two-thirds of sources are very familiar with Tyvaso, with all but one of the remaining eight sources somewhat familiar. "I am mostly familiar based on data presented at meetings and conversations with investigators participating in the clinical trial," said a source at a hospital university center. Meanwhile, more than three-fourths of sources are very familiar with Adcirca, with the remaining sources somewhat familiar. "I'm intimately familiar with this [drug]," a pulmonologist said.

Just a few weeks post launch, more than one-half of sources have been detailed by United Therapeutics on Tyvaso. "I bumped into the rep back in August, and he told me a bit about it. He said he'll come back this month," said a source at a center in Florida. The remaining sources have not been detailed but expect to be detailed soon. "I asked to be detailed, but they said they can't do that until the launch. They're just following the rules," one said. A handful of sources also had been counter-detailed by Actelion. "[Actelion was] very willing to talk about the negatives of the device for Tyvaso," a pulmonologist said.

Widespread Adoption Expected for Tyvaso, Adcirca

Tyvaso's adoption is expected to be rapid and widespread, with nearly two-thirds of sources expecting to start prescribing the drug immediately, and all but one expect to use it within three months. "[I'll prescribe Tyvaso] as soon as it is available commercially," one said. A physician with 150 PAH patients under his care said, "I'll start any time now. We have research patients already on it." Similarly, Adcirca's adoption also is expected to be rapid and widespread, with 20 of 24 expecting to start prescribing it immediately and the remainder expecting to use it within three months. "I've tried [Adcirca] already, so I'm just waiting for pharmacies to stock it," a source said.

Although Tyvaso and Adcirca prescription volumes are low, both are set to experience a robust surge in use through mid-2010. Sources have only three patients on Tyvaso so far, but this is expected to ramp to 180 by year-end and to 419 by mid-2010, representing 5%–7% and 12%–14% of their PAH patients, respectively. "I will offer it to appropriate patients right after becomes available," one said. Another said, "I'll definitely be using it within the next few months."

Adcirca is expected to experience a similarly robust increase — from 35 patients now to 311 by year-end and to 958 by mid-2010, representing 9%–11% and 29%–31% of their PAH patients, respectively. "We intend to offer Adcirca to 100% of our [current] Revatio patients," said a source treating 700 PAH patients.

"I bumped into the rep back in August, and he told me a bit about it. He said he'll come back this month."

Source at a center in Florida

TYVASO DETAILING UNDERWAY

PRESCRIPTION RAMP STRONG

PAH Treatments

Switches, Oral Drug Patients Main Tyvaso Pool

Almost all sources said patients who will receive Tyvaso likely will be those progressing on oral treatments. “Patients with unsatisfactory response to oral therapies or with progressive disease despite oral therapies [will likely be prescribed Tyvaso],” a pulmonologist said. Another said, “Patients progressing on orals would have the option of Tyvaso.” Almost two-thirds also expect to switch some patients on Ventavis to Tyvaso. “We’ll consider switching some from Ventavis. If they’re doing all right and don’t want to switch, that’s patient preference, but we’ll certainly provide the information and that option,” said a cardiologist with more than 300 PAH patients under his care. Another source said she would switch patients from Ventavis but only if they were noncompliant with Ventavis treatment, saying, “My biggest concern is that it’s a newer drug and the indications they’ve approved it for aren’t as strong as other drugs.” Slightly more than one-third also would consider Tyvaso for patients who have not had any previous treatment for PAH. “The largest group will be treatment-naive patients,” said a source at an East Coast center.

Ventavis Prescribing Likely to Take Big Hit

Tyvaso’s launch is likely to have the largest impact on Ventavis, with two-thirds of sources expecting Tyvaso to have a major impact on Ventavis prescribing, and four more saying it would have a moderate impact. The number of patients being prescribed Ventavis is expected to fall from current levels of 191 to 132 at year-end, a 30%–32% decline in prescription volumes, with further decrease expected through mid-2010. “Tyvaso will have a big impact on Ventavis. Tyvaso will be more attractive to patients. If it’s equally priced or [has a] decreased price, it will corner the market,” a pulmonologist said. Another said, “Ventavis will be severely affected. [Tyvaso] will take over a major portion of [Ventavis’ share]. It will be easier to use.”

Although Tyvaso is an inhaled formulation of Remodulin, 22 of 24 sources said Tyvaso will have little to no impact on Remodulin prescribing. “There will be no or little impact on Remodulin; once they’re on IV or sub-Q, the only reason we’d switch would be if there are infection or other problems with needle or administration,” said a director of PAH services. Sources have 446 patients on Remodulin, and this is expected to increase to 498 by year-end and to 635 by mid-2010.

Dosing Convenience Main Advantage for Both

All but one source said Tyvaso’s main advantage is more convenient dosing. Patients on Ventavis need to inhale the treatment up to nine times a day, with each treatment taking 10–20 minutes, while Tyvaso only needs to be dosed four times per day at less than five minutes per treatment. “Tyvaso has less frequent and shorter time to administer than Ventavis. More patients potentially might be amenable to this form of therapy,” a source said. A PAH specialist said, “[Tyvaso] is great. It has a more convenient dosing frequency and takes less time to administer [than Ventavis].” Others said it would significantly improve treatment compliance. “The lower dosing frequency will obviously have an impact on better compliance,” said a source from a university medical center. Another source said, “More convenient dosing is the biggest issue; it’s very important. Less frequent dosing translates to more compliance in patients.” Most sources also said Adcirca’s main benefit is its more convenient dosing schedule. “Once-a-day dosing makes it very helpful,” said one. “These patients are on many medications and the less frequent the dosage, the more compliant [they will be].”

“We’ll consider switching some from Ventavis. If they’re doing all right and don’t want to switch, that’s patient preference, but we’ll certainly provide the information and that option.”

Cardiologist

REMODULIN USE

PAH Treatments

Adcirca Drawing Revatio Switches, New Patients

Adcirca likely will draw new PAH patients as well as switches from Pfizer's Revatio, according to most sources. "I will likely prescribe Adcirca to switches from Revatio and new patients [who are] likely to be noncompliant with twice-daily meds," said an internal medicine specialist. A cardiologist said, "I'll definitely use it for new starts and patients having difficulty taking meds three times a day." Sources expect 81%–83% of patients starting on a PDE-5 inhibitor to be given Adcirca rather than Revatio. "I will probably try all of them on Adcirca first because it is cheaper and compliance should be better. It is a better drug overall. I probably won't use Revatio at all," one said. Another said, "Revatio is about dead as far as our practice is concerned. We're moving everyone over to Adcirca." More than one-third of sources said patients progressing on oral treatment may also be suitable for Adcirca, but only as part of combination therapy since Adcirca is considered a first-line PAH treatment. "I may be adding Adcirca to Tracleer and Letairis," one said.

Tyvaso Device Could Prove Stumbling Block

The device used to deliver Tyvaso could prove cumbersome, according to more than one-half of sources. "The device has several parts, and it's much more challenging than its competitor, but the FDA is asking the company to make some adjustments," said a PAH clinic's director. United Therapeutics is working a new inhaler device, which is expected to be available in 2H10 and may alleviate source concerns with the present device. "The module they have to carry is cumbersome. They need to make this into a better device," one said. Two sources felt the fiddly and unwieldy device could restrict which patients Tyvaso is suitable for. "PAH is mostly in the younger population, with many in their 20s and 30s, and they're more adaptable," one said.

Sources were less certain of the potential downsides likely with Adcirca treatment, although one-third said headache could be a potential side effect. "One side effect that is pretty significant with Adcirca is headache," a pulmonologist said. Another said headache could be severe enough in some patients to warrant stopping treatment. "I'm concerned that 50% of patients are reporting significant headaches, and that's not a problem with Revatio. If patients experience severe headaches, we may have to stop Adcirca," the source said.

Tyvaso Reimbursement Unclear

There was no clear consensus among sources how Tyvaso reimbursement will play out. One-third did not know how reimbursement would be for Tyvaso, but several said it could be similar to Ventavis. "I believe [Tyvaso] will be reimbursed just like Ventavis as long as [it's] not priced much over Ventavis," said a source. Another said it may work out to be cheaper than Ventavis. However, a handful of sources anticipate that reimbursement could be difficult. "I am sure [reimbursement] initially will be a problem. The good thing is United has a good patient assistance program. In the long run, though, it will be OK," a nurse practitioner said. Another source said, "I expect we'll have to jump through hoops with this as with any other, but some of my patients will still end up needing subsidiary help."

This report was researched and written by **Charlotte Waterworth**, with additional reporting from **Rachel Kelley**, **Kate Kitchen** and **Clementine Wallace** for OTR Global LLC.

"Revatio is about dead as far as our practice is concerned. We're moving everyone over to Adcirca."

ADCIRCA HEADACHES

PAH Treatments

ON TYVASO AND ADCIRCA ADOPTION

"The rep will come in this month, so we will prescribe Tyvaso shortly after that."

"I have a Remodulin patient who can't take it, who needs to be changed to Tyvaso, so I'll use it ASAP."

"I'm already prescribing Adcirca. It's been available for several weeks."

"We just started converting some patients [to Adcirca]."

ON PATIENTS WHO WILL RECEIVE TYVASO

"It may be suitable for patients who are on oral treatments that are progressing, but it depends on the side effects."

"[Tyvaso will be for] patients with unsatisfactory response to oral therapies or with progressive disease despite oral therapies and switches from Ventavis."

"I might add [Tyvaso] on to [Actelion's] Tracleer, so, yes, I will use it for patients progressing on oral PAH treatments."

ON PATIENTS WHO WILL RECEIVE ADCIRCA

"We have a constant influx of new PAH patients, so we'll try this on new starts first."

"I will give a lot to new patients and possibly transition Revatio patients that are on 20 mg three times a day."

"Many will be new starts [treatment naive patients or add-on to other classes of medication]; some will be switches from Revatio."

ON TYVASO, ADCIRCA ADVANTAGES

"There are less frequent inhalations [with Tyvaso] compared to Ventavis."

"Tyvaso is a regimen of fewer treatments and much less time per treatment."

"How fast [Tyvaso] can be delivered is a decided advantage to keep patients compliant."

"Once a day [dosing of] Adcirca is the biggest deal."

"[Adcirca represents] less pills, fewer times a day and at a lower cost than Revatio."

"The big advantage [of Adcirca], besides once-a-day therapy, is that dosage is higher and more appropriate."

ON TYVASO, ADCIRCA DISADVANTAGES

"I hear the Tyvaso inhaler is cumbersome and has many parts."

"The device is a little more complicated. There are more pieces you have to put together."

"I've played with the [Tyvaso] device and I can put it together, but that's one thing the competitors will say about it. It's kind of funky."

"One side effect that is pretty significant with Adcirca is headache."

"Adcirca reportedly has more headaches [frequency and side effects], so I am concerned about tolerability; I will see over the next few months."

ON TYVASO REIMBURSEMENT

"I have no idea [about reimbursement]. I expect it will be as expensive as Ventavis. I heard from other doctors that it's expected to cost \$100,000 a year."

"Reimbursement will probably be similar to other meds."

PAH Treatments

“It’s not simple for Ventavis, but I don’t expect any problems with Tyvaso.”

ON TREATMENTS THAT WILL LOSE OUT TO TYVASO

“Ventavis will probably be hit the most. The question is whether there are going to be any head-to-head studies comparing the two drugs.”

“Ventavis will be hit moderately at first, I think, but later on, once results are proven, I think it will change to a major impact.”

“The only drug I can see it having an impact on is Ventavis, but just not with me. My patients have compliance issues with the frequency of Ventavis therapy, so I almost completely have stopped using it.”

“It will affect Ventavis and any other prostacyclins.”

PAH Treatments

1. Approximately how many PAH patients are you treating?

500 or more:	1
300–349:	1
250–299:	2
200–249:	1
180–199:	1
160–179:	2
140–159:	3
120–139:	1
60–79:	1
40–59:	6
20–39:	2
1–19:	3
Total:	3,344

2. How familiar are you with United Therapeutics' Tyvaso and Adcirca?

Very familiar:	16
Somewhat familiar:	7
Not familiar:	1

3a. What are the advantages of prescribing Tyvaso compared with existing PAH therapies? (Some sources gave more than one answer, and others did not respond.)

More convenient dosing frequency:	23
Short admin time:	11
Better efficacy:	1
Better patient compliance:	1
Second line treatment:	1
Treatment half life:	1

3b. What are the disadvantages of prescribing Tyvaso compared with existing PAH therapies? (Some sources gave more than one answer, and others did not respond.)

Cumbersome inhalation device:	14
Cough:	2
Dose titration difficult:	1
Long-term effects unknown:	1
Potential high cost:	1
Some data not very impressive:	1

4. To which of your PAH patients are you likely to prescribe Tyvaso? (Some sources gave more than one answer)

Patients progressing on oral PAH treatments:	20
Switches from Ventavis:	14
Treatment-naïve patients:	9
Switches from Remodulin (IV and SQ):	8
Adjunct therapy:	4
Patients unable to tolerate IV:	2
Patients unable to tolerate prostin routes:	1
Don't expect to prescribe in near future:	1
Type 1 PAH:	1

5a. Have you been detailed on Tyvaso by a United Therapeutics sales rep?

Yes:	14
No:	10

PAH Treatments

5b. Have you been counter-detailed on Tyvaso by an Actelion rep?

Yes:	5
No:	19

6. How do you expect reimbursement will be for Tyvaso?

Major positive:	2
Minor positive:	2
Neutral/no effect:	6
Minor negative:	5
Don't know:	9

7. How quickly do you expect to begin prescribing Tyvaso?

Immediately upon launch:	15
Within 3 months:	8
No plans to prescribe:	1

8. Which competing PAH treatments do you expect to be affected by Tyvaso's launch?

	REMODULIN	VENTAVIS	REVATIO	ADCIRCA
Major impact:	1	16	1	-
Moderate impact:	1	4	1	-
Minor impact:	11	2	4	5
No impact:	11	2	18	19

9. How familiar are you with United Therapeutics's Adcirca?

Very familiar:	19
Somewhat familiar:	5

10a. What are the advantages of prescribing Adcirca compared with existing PAH therapies? (Some sources gave more than one answer, and others did not respond.)

More convenient dosing frequency:	21
Can be dosed at optimal dose:	3
Lower cost:	3
Treatment half life:	2
Better efficacy:	1
No significant drug interactions:	1
Other:	1

10b. What are the disadvantages of prescribing Adcirca compared with existing PAH therapies? (Some sources gave more than one answer, and others did not respond.)

Headache:	7
Appropriate dosage unknown:	2
Getting it approved:	2
Efficacy:	1
Long-term effects unknown:	1
New to the market/no history:	1
No different from Sildenafil:	1
None:	2

PAH Treatments

11. To which of your PAH patients are you likely to prescribe Adcirca? (Some sources gave more than one answer.)

Patients switched from Revatio:	22
Newly diagnosed PAH patients:	21
Patients progressing on other oral drugs:	10
Patients progressing well on IV therapy:	2
Don't know:	1

12. What do you expect your breakdown between Revatio and Adcirca to be for the patients you start on this category of drug (i.e. a PDE 5 inhibitor)

	REVIATIO	ADCIRCA
91%–100%:	-	7
81%–90%:	-	2
71%–80%:	-	5
51%–60%:	1	2
41%–50%:	5	5
31%–40%:	2	1
21%–30%:	2	-
11%–20%:	3	-
1%–10%:	4	-
0%:	5	-
Don't know:	2	2
Weighted average:	16%–21%	79%–84%

13. How quickly do you expect to begin prescribing Adcirca?

Immediately upon launch:	20
Within 3 months:	4

14a. To approximately how many PAH patients are you prescribing Remodulin (IV and SQ), and what do you expect these numbers to look like at year-end and mid-2010?

	CURRENT	DECEMBER 2009	MID-2010
101 or more:	1	1	1
71–80:	-	-	2
61–70:	-	1	-
51–60:	2	2	2
41–50:	2	1	1
21–30:	-	2	1
11–20:	5	6	6
1–10:	9	7	7
0:	4	3	3
No response:	1	1	1
Total:	446	498	635
PAH patient penetration:	13%–15%	15%–17%	19%–21%

14b. To approximately how many PAH patients are you prescribing Tyvaso, and what do you expect these numbers to look like at year-end and mid-2010?

	CURRENT	DECEMBER 2009	MID-2010
91–100:	-	-	2
51–60:	-	-	1
31–40:	-	1	-
21–30:	-	2	2
11–20:	-	1	1
1–10:	1	18	16
0:	22	1	1
No response:	1	1	1
Total:	3	180	419
PAH patient penetration:	Less than 1%	5%–7%	12%–14%

PAH Treatments

14c. To approximately how many PAH patients are you prescribing Ventavis, and what do you expect these numbers to look like at year-end and mid-2010?

	CURRENT	DECEMBER 2009	MID-2010
51-60:	-	-	1†
41-50:	1	2†	1
31-40:	1†	-	-
21-30:	2	-	-
11-20:	1	2	1
6-10:	5*	2	2
1-5:	12	16*	15
0:	1	1	3
Don't know:	-	-	1*
No response:	1	1	1
Total:	191	132	122
PAH patient penetration:	6%-8%	4%-6%	3%-5%

* One source who did not provide answers to all three time periods excluded from total calculations

† One outlier source removed from total calculations

14d. To approximately how many PAH patients are you prescribing Adcirca, and what do you expect these numbers to look like at year-end and mid-2010?

	CURRENT	DECEMBER 2009	MID-2010
101 or more:	-	-	1
91-100:	-	-	1
61-70:	-	-	1
51-60:	-	-	3
41-50:	-	1	-
31-40:	-	2	1
21-30:	-	4	-
11-20:	-	-	5
1-10:	8	16	11
0:	15	-	-
No response:	1	1	1
Total:	35	311	958
PAH patient penetration:	0%-2%	9%-11%	29%-31%

PAH Treatments

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