

First deuterated drug approved

In April, the US Food and Drug Administration cleared the first deuterated drug, Austedo (deutetabenazine), from Teva of Petach Tikva, Israel, for the treatment of Huntington's-disease-related movement disorders. Austedo is also the first new treatment in over a decade for this indication. Deuteration has come in and out of fashion for more than 50 years and recently companies have started to pay big sums for heavy-hydrogen drugs. Teva acquired rights to Austedo through its \$3.5-billion purchase of Auspex Pharmaceuticals, in May 2015. More recently, in March 2017, Concert Pharmaceuticals of Lexington, Massachusetts, sold its deuterated Kalydeco (ivacaftor) for treating cystic fibrosis to Vertex Pharmaceuticals of Boston for \$160 million in cash and \$90 million in potential milestones and royalties. In theory, incorporating 'heavy hydrogen' into small molecules makes a drug last longer and improves its toxicity profile. But some question their meager clinical advantages and whether the intellectual property for a deuterated drug is defensible.

For decades, chemists have been using deuterium, a heavy isotope of hydrogen, to tweak medicinal compounds and improve their pharmacokinetic and toxicity profiles. Now, Austedo's approval "establishes a clearer pathway for how other deuterated compounds can reach the market," says Graham Timmins, an associate professor at the College of Pharmacy at the University of New Mexico, in Albuquerque, New Mexico, in March 2017. But whether deuterated drugs deliver clinical advantages to patients remains unclear. Skeptics argue that these modifications, instead, provide drugmakers with a brand new therapeutic compound and the opportunity to extend an old drug's patent life.

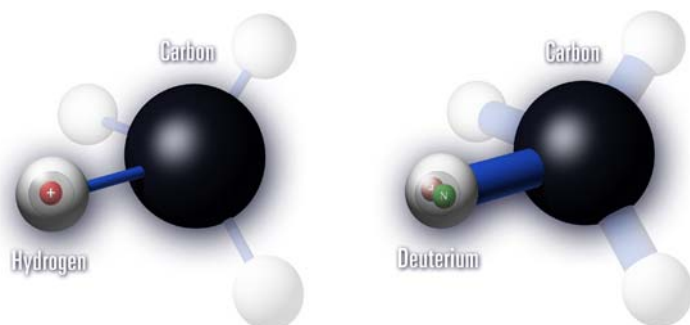
Deuterated drugs swap hydrogen atoms for deuterium at selected locations in the molecular structure. With that chemical change, modified drugs can resist metabolic degradation and remain active for longer in the body than

the parent compound. Austedo is modified tetrabenazine—a drug that targets the vesicular monoamine transporter type 2, a transport protein on presynaptic neurons. Tetrabenazines have been a mainstay in Huntington's treatment for decades. They act by depleting the monoamines dopamine and serotonin, and other monoamine neurotransmitters, helping to reduce the involuntary writhing associated with the disorder.

To be effective and to reach peak concentrations, tetrabenazines must be given three times per day. During Austedo's placebo-controlled phase 3 clinical trial, 90 patients took two daily doses to reduce the disease symptoms. Lowering the dose also meant tetrabenazine side effects, such as sleepiness, depression and anxiety, also lessened.

Michael Geschwind, co-director of the Huntington's Disease Center of Excellence at the University of California, San Francisco, who was not involved in the clinical trial but published an editorial about it last year (*JAMA* **316**, 33–35, 2016), says Austedo led to a range of clinical improvements. As both drugs, if dosing is taken, will cost roughly the same, Geschwind thinks physicians will opt for the deuterated drug because its side effect profile is more benign than that of tetrabenazine. The wholesale acquisition price for Austedo at \$60,000 per year is based on a dose of 24 milligrams per day. The dose equivalent for generic tetrabenazine is approximately \$48,000 a year.

A handful of deuterated compounds are now in the clinic for various indications (**Table 1**). Deuterated drugs are heavier drugs than their unmodified counterparts. This is because the deuterium nucleus has a proton and a neutron (instead of hydrogen's single proton), which doubles its atomic mass. Chemists introduce deuterium at strategic sites in the molecular structure, resulting in compounds with deuterium-carbon bonds that are up to ten times stronger than the hydrogen-carbon bonds. This helps protect deuterated compounds from



Concert

Heavy isotopes make stronger bonds. Deuterium is a stable, non-radioactive isotope of hydrogen.

enzymatic degradation in the liver, increasing the compound's half-life.

Still, deuterated compounds can in some instances behave unpredictably. They might be skewed toward producing toxic metabolites as opposed to harmless ones, necessitating diligent risk management and efforts to predict how metabolic enzymes, such as CYP-450, and, in Austedo's case, CYP2D6, will process the drug. Indeed, after raising concerns about Austedo's potential toxicity last year, the US Food and Drug Administration (FDA) sent Teva back with a complete response letter to reanalyze the drug's metabolites in blood, delaying approval for nine months before approving the drug on April 3, 2017.

Whether Austedo is superior to tetrabenazine would require a head-to-head trial, and this has not been done. But Auspex researchers measured active metabolites from the two compounds during a pharmacokinetic study with healthy volunteers and reported in 2013 that those generated by deuterated tetrabenazine lasted twice as long in the body. This characteristic means that deuteration preserves the therapeutic benefit for longer and with lower doses (*JAMA* 316, 40–50, 2017). Claudia Testa, an associate professor at Virginia Commonwealth University and a co-investigator on the Austedo phase 3 trial, says the reduced dose needed with a deuterated agent could help reduce side effects, such as grogginess or restlessness. "That's what we anticipate, but we won't know for sure until we see how the drug works in the general population of Huntington's patients," she says.

Next in line is Concert's AVP-786, a deuterated form of the cough suppressant dextromethorphan. The drug's activity is through its major metabolite, dextrorphan. Undeuterated extromethorphan is also an *N*-methyl-*D*-aspartate (NMDA) receptor antagonist, which the FDA approved in combination with the drug quinidine to treat involuntary crying or laughing spells that afflict patients with brain injuries and neurologic disease. Quinidine slows dextromethorphan's breakdown to allow high therapeutic levels to accumulate. But quinidine also has troubling cardiovascular side effects at higher doses. So, Avanir Pharmaceuticals of Aliso Viejo, California, the company marketing the undeuterated combination as Nuedexta, partnered with Concert to combine quinidine with the more stable deuterated AVP-786. "With deuterated dextromethorphan you can give less quinidine," explains Concert's founder and CEO, Roger Tung. The quinidine–AVP-786 combination is currently in phase 3 for treating agitation in Alzheimer's patients and in phase 2 for depression and schizophrenia.

Table 1 Selected deuterated compounds in clinical development

Drug maker	Drug name	Deuterium-modified drug	Target	Indication	Status
Avanir/Concert	AVP-786	Dextromethorphan	NMDA glutamate receptor	Alzheimer's disease agitation symptoms	Phase 3
				Depression/schizophrenia	Phase 2
Concert	CTP-543	Ruxolitinib	JAK/STAT	Hair loss (alopecia aerate)	Phase 2
Vertex	CTP-656	Kalydeco (ivacaftor)	CF transmembrane conductor regulator	Cystic fibrosis	Phase 2
DeuteRx	DRX-065	Pioglitazone (deuterated form)	(PPAR- γ)	Non-alcoholic steatohepatitis/adrenoleukodystrophy	Phase 1
Retrotope	RT001	Linoleic acid	Cell membrane	Freidreich's ataxia	Phase 1/2
BMS	BMS-986165	New molecular entity	Tyrosine kinases	Psoriasis	Phase 2
Celgene/Concert	CT-730	Apremilast	PDE4	Inflammatory disorders	Phase 1
Vertex	VX-984	Doxorubicin	DNA-dependent protein kinase	Solid tumors	

Concert is also developing a deuterated form of Vertex's approved cystic fibrosis (CF) drug Kalydeco (ivacaftor). The agent, dubbed CTP-656, which now belongs to Vertex, is currently in phase 2 as monotherapy for cystic fibrosis patients with G551D mutations. As with Austedo, CTP-656 needs less frequent dosing, from twice to once a day, and, unlike Kalydeco, does not have to be taken with a fatty meal for optimal absorption.

Introducing heavy hydrogen has other benefits, besides boosting drug half-lives. It is possible to use deuterium to stabilize enantiomers of a drug into a desired orientation. Enantiomers often flip between mirror images of each other; each can have vastly different properties. Thalidomide, for instance, is a mixture of two enantiomers, the right-handed *R* and the left-handed *S*. It was approved in Europe decades ago as a treatment for morning sickness in pregnant women, but the women who took the drug had babies with horrific birth defects. Scientists later discovered the *S* enantiomer was the likely cause of these teratogenic effects, while the *R* enantiomer was therapeutic. A number of companies today, like Retrotope of Los Altos, California, employ deuterium to stabilize enantiomers in a single therapeutic orientation. The company, which is developing fatty acids to fortify cell and mitochondrial membranes against oxidative damage, has taken its lead compound, a deuterated form of linoleic acid, into a phase 1/2 clinical trial for treating Freidreich's ataxia, an inherited and progressive disease of the central nervous system.

DeuteRx, in Andover, Massachusetts, swaps deuterium for hydrogen in the chiral center, to stabilize a drug of a single desired enantiomer. Its lead compound, DRX-065, is the *R* enantiomer of pioglitazone, stabilized with

deuterium. Widely used as a generic diabetes drug, and also used off-label in patients with non-alcoholic hepatosteatosis (NASH), pioglitazone frequently induces weight gain and edema. However, only the *S* enantiomer of the drug causes these side effects. The *R* enantiomer, which works through an alternate mitochondrial pathway, does not. DRX-065 is now in phase 1 for adrenomyeloneuropathy and also for NASH.

There are critics who see companies' enthusiasm for deuteration as a way to extend patent life without investing heavily in new treatments. Sheila DeWitt, president and CEO of DeuteRx, notes that because deuteration generates entirely new chemical entities, the new composition matter does support patent applications. Indeed, beginning in the late 1990s, some new firms set out to patent deuterated versions of existing drugs, while large pharma companies retaliated by doing the same with their own products. Timmins says the patent rush has slowed with deuteration now becoming a standard (or in patent language "obvious") aspect of drug development. "Once you start doing this it becomes normal state of the art instead of real innovation," he says.

Auspex's founder Tom Gant, now a private consultant with Recondite Falls Discovery, a firm specializing in deuterium substitution, located in Hudson, Florida, worries that drug companies have yet to tap into the more promising opportunities afforded by deuteration, such as reducing toxicity. Timmins agrees, and says the primary benefit from deuteration demonstrated so far appears to be reducing the daily dosing. "Whether that's a benefit worth paying for is something the payers will have to decide," he says.

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Corrected after print 13 April 2018.

Erratum: First deuterated drug approved

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In the version of this article initially published, the drug BMS-986165 was listed as a “deuterium-modified” version of rosuvastatin, rather than a “deuterium-modified” new molecular entity. The error has been corrected in the HTML and PDF versions of the article.