14-4624(cv)

In the
United States Court of Appeals for the Second Circuit

STATE OF NEW YORK, by and through
ERIC T. SCHNEIDERMAN, Attorney General

Plaintiff-Appellee,

v.

ACTAVIS PLC & FOREST LABORATORIES, LLC

Defendants-Appellants.

ON APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK (SWEET, D.J.)

PAGE PROOF BRIEF OF PHYSICIAN *AMICI CURIAE* IN SUPPORT OF DEFENDANTS-APPELLANTS

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STATEMENT OF INTEREST OF THE AMICI CURIAE[1]

The *amici curiae* are experienced physicians specializing in the care of patients with Alzheimer's Disease. As physicians providing care in this field, the *amici* have a direct interest in addressing legal developments, such as the nationwide injunction issued by the district court below, that may have an impact on the availability of new and improved medicines or the quality of patient care in this field. The *amici* also view the district court's order as resting on certain erroneous medical conclusions and believe that their extensive experience with Alzheimer's patient care and therapeutics may assist the Court in its consideration of the appeal.

The *Amici*

Alireza Atri, M.D., Ph.D. is an Alzheimer's disease caregiver and a cognitive neurologist specializing in the care of individuals with memory disorders and dementias. Dr. Atri serves as Assistant in Neurology in the Memory Disorders Unit and the Alzheimer's Disease Research Center at Massachusetts General Hospital, and is an Instructor in Neurology at Harvard Medical School. Dr. Atri

[1] This brief is filed with the written consent of all parties. No counsel for a party authored this brief in whole or in part, nor did any person, other than the *amici* or their counsel, make a monetary contribution to the preparation or submission of this brief.

has taught and published extensively on Alzheimer's disease and the effectiveness of Alzheimer's medications in the real-world setting.

Carl Sadowsky, M.D. is clinical professor of neurology at Nova Southeastern University. Dr. Sadowsky has 35 years of clinical experience in Alzheimer's Disease and has been selected as one of the Best Doctors in America for the past ten years. He has been involved in numerous clinical trials evaluating the safety and efficacy of Alzheimer's drugs, was principal investigator on two leading clinical trials that led to the approval of the drug Memantine, and is a board member of the Southeast Florida Alzheimer's Association. He is on the advisory board of several corporations developing new drugs for the treatment of Alzheimer's disease.

James E. Galvin, M.D., M.P.H. is Professor of Neurology, Psychiatry, and Population Health at the New York University Medical School, where he is also the Director of New York State-funded Alzheimer's Disease Assistance Center and Associate Director of the NIH-funded Alzheimer's Disease Center. Dr. Galvin has published more than 140 scientific papers and more than 20 book chapters covering basic, clinical, and translational science in the area of neurodegenerative disorders, dementia, and cognitive aging; is the editor of three textbooks on dementia; and serves on the editorial board for three journals.

Gustavo Alva, M.D. is the medical director of ATP Clinical Research, a premiere private clinical research company specializing in neuropsychiatric investigations. He previously served as Associate Professor and Deputy Director of Clinical Research in the Department of Psychiatry and Human Behavior at the University of California, Irvine. Dr. Alva has served as a principal investigator since 1995 for studies of neuropsychiatric conditions including Alzheimer's Disease and has published widely in the field.

SUMMARY OF THE ARGUMENT

The *amici curiae* respectfully submit this brief to express serious concerns regarding certain key factual and legal conclusions underlying the district court's injunction below, and the policy implications of those conclusions and of that injunction. Specifically, the *amici* believe that the district court disregarded or gave insufficient weight to compelling evidence that (i) Namenda XR provides a substantial benefit over Namenda IR, (ii) switching from the IR to the XR formulation (and back) causes no harm to patients, and (iii) physicians remain able, both now and in the future when generics become available, to prescribe the older IR formulation if they consider it appropriate for whatever reason. By reaching contrary and erroneous conclusions on these points, the district court has entered an order that may have detrimental effects on drug discovery, development, and availability and, hence, clinical therapeutics and patient care in this field.

If an order like the one below, well-intentioned but based on mistaken scientific and medical conclusions, discourages incremental improvements of existing drugs or drug formulations by removing vital financial incentives, or reduces the availability of newer and better drugs or drug formulations by forcing older outmoded drugs back into the main production and distribution channels, the losers will be the very patients whom the district court's order seeks to protect, and the caregivers on whom they depend. At the same time, the *amici* do not view the injunction as helping their patients or their caregivers: its rationale seems to be to ensure the availability of Namenda IR, but Namenda IR is readily available to any patients who need it and, as we understand it from Forest's public announcements, would remain so over the next six months and thereafter without the injunction.

ARGUMENT

I. THE DISTRICT COURT WRONGLY CONCLUDED THAT XR CONFERS NO SIGNIFICANT BENEFIT OVER IR

The record below is clear that once-daily dosing provides a substantial benefit to Alzheimer's patients and their caregivers, *inter alia*, by facilitating adherence to their prescription regimens and reducing the associated care burden. That conclusion accords both with the experience of the *amici*, who grapple regularly with the difficulties of prescription adherence and pill burden, and with a consistent body of medical literature and expert opinion reflecting the problem of

adherence, particularly for Alzheimer's disease patients, and demonstrating the adherence benefits of once-daily formulations. For example:

- G. Small & R. Bullock, "Defining Optimal Treatment with Cholinesterase Inhibitors in Alzheimer's Disease," in Alzheimer's & Dementia 177-184 (2010) ("[T]he AD population (including caregivers) is particularly susceptible to poor compliance. They have a tendency to be plagued by risk factors, such as advanced age, co-morbidities, high-medication burden and memory deficits. . . . Considering the established importance of compliance in AD therapies in the long-term, a clear need exists to improve compliance in this setting.");

- G. Small & B. Dubois, "A Review of Compliance to Treatment in Alzheimer's Disease: Potential Benefits of a Transdermal Patch," 23 Current Med. Research & Op. 2706 (2007) ("Positive clinical outcomes, such as delaying the worsening of functional, cognitive and behavioral symptoms, can only be achieved with sustained medication use. However, treatment management represents a major challenge for patients with AD and their caregivers, and noncompliance is often a barrier to effective therapy.");

- R. Brady & J. Weinman, "Adherence to Cholinesterase Inhibitors in Alzheimer's Disease: A Review," 35 Dement. Geriatr. Cogn. Disord. 351–363 (2013) (discussing problem of adherence in Alzheimer's patients and various factors affecting adherence, including caregiver stress and ease of medication administration);

- N. Campbell et al., "Medication Adherence in Older Adults with Cognitive Impairment: A Systematic Evidence-Based Review," 10 Am. J. Geriat. Pharmacotherapy 165-177 (2012) (discussing impediments to adherence such as memory, medication knowledge, health literacy, concern for adverse effects, and cost);

- S. Travis et al., "Medication Administration Hassles Reported by Family Caregivers of Dependent Elderly Persons," 55 J. Geront.: Med. Sci. M412 - M417 (2000) (describing problems faced by caregivers in giving medications, including administration and scheduling, and calling for "continual re-evaluation and

simplification of medication regimens for dependent elderly persons in family care situations.");

- L. Brewer et al., "A Population-Based Study of Dosing and Persistence with Anti-dementia Medications," 69 Eur. J. Clin. Pharm. 1467–1475 (2013) (study of prescription-claims database of 1.6 million people; patients who received at least two prescriptions for the Alzheimer's drugs donepezil, rivastigmine, galantamine, or memantine were more adherent to once-daily formulations.);

- G. Grossberg et al., "The Safety, Tolerability, and Efficacy of Once-Daily Memantine (28 mg): A Multinational, Randomized, Double-Blind, Placebo-Controlled Trial in Patients with Moderate-to-Severe Alzheimer's Disease Taking Cholinesterase Inhibitors," CNS Drugs 27: 469–478, 470 (2013) ("Considering the problems associated with poor medication adherence in AD, the availability of an extended-release, once-daily memantine formulation would be expected to provide improved convenience, and may potentially enable an increased daily dosage without affecting the drug's favorable safety and tolerability profile.");

- JA __ (Dr. Reisberg Hrg. at 727-728[2]) ("There is an exponential difference between being able to take a medication once daily versus twice daily. . . . [T]hese differences become very much compounded for my patients.");

- JA __ (Dr. Kohrman Hrg. at 761) (The "once a day medication is a superior product for all the reasons we've talked about, especially reducing care giver burden and ease of administration.");

- JA __ (Dr. Reisberg Hrg. at 734) (Namenda XR tablets are "superior in the sense that they only need to be given once a day.");

- JA __ (Dr. Kohrman Hrg. at 740) ("[T]here have been various studies actually done looking in Alzheimer's patients at caregiver burden as you move from multiple-times-a-day dosing to once-a-day dosing,

[2]All hearing testimony can be found at Pace Decl. Ex. 1, attached to Actavis' Motion to Stay (Dkt. 41-1).

> and the studies have supported this and it has been my clinical experience.").

Nonadherence and the importance of reducing pill burden are some of the most basic challenges of Alzheimer's care, familiar to anyone who has served this patient population. The term "adherence" (also known as "compliance") as used in this context refers to the fact that patients benefit from medications only when they actually take them, and do so as prescribed. Nonadherence is widespread among Alzheimer's patients, who suffer from cognitive dysfunction, including deficits in memory, insight, foresight, judgment, and executive function, as well as, frequently, neuropsychiatric (*e.g.*, delusions), emotional, and psycho-social dysfunction, which in turn result in inability to consistently self-administer medications, and, often, resistance to taking the prescribed medications when they are presented by caregivers. "Pill burden" refers to the added cost, difficulty, and adherence implications of taking a larger number of medications, particularly if they have to be taken at multiple times during the day. Adherence and pill burden are important considerations in the care of Alzheimer's patients. Once-daily formulations can provide a substantial benefit, particularly for patients suffering from dementia, for this reason.

It is surprising that, after acknowledging the benefits of once-daily dosing, the district court's order appears to adopt a contrary view, *i.e.*, that once-daily dosing does not provide a significant benefit for dementia patients. *See* SA-54-56

(P.I. Op. ¶¶ 82-84, 86). The court, for example, acknowledges that there is an "exponential" difference between "being able to take a medicine once daily versus twice daily," that this benefit is "very much compounded for" Alzheimer's patients, that "[f]ewer pills generally lead to greater compliance with treatment," that "'[m]any controlled clinical trials ha[ve] also shown the 'extended release agents are associated with improved, tolerability, greater patient adherence to treatment, reduced total treatment cost, and better long-term clinical outcomes,'" and that "sundowning" and agitation "'may make it more difficult to get the patient the medication they need,'" SA-35-36 (P.I. Op. ¶¶ 46-47). Yet, later in its opinion, the court concludes, incongruously, that the benefits are "often marginal" and that "being able to take Namenda once a day instead of twice, is not a significant benefit for patients already taking other twice-daily medications."[3] SA-54 (P.I. Op. ¶ 82). The *amici* are not aware of any research or scientific evidence supporting this view, which contradicts their clinical experience and the relevant literature.

The principal, and in substance the sole, evidentiary basis for the district court's conclusions, is the testimony and declaration of Dr. James Lah, who states

[3] Many Alzheimer's patients are not on twice-daily medications, and, when they are, the *amici* try to work with the other prescribers to simplify their regimens. Inconsistency in taking other medications can also adversely affect the management of Alzheimer's symptoms in various ways depending on the type of medication (*e.g.*, by causing fluctuations in blood pressure or glucose levels).

that, "[i]n my [clinical] experience, compliance has not been a problem." JA __ (Dr. Lah Decl. ¶ 15); *see also* SA-54 (P.I. Op. ¶ 82). That is not the experience of the *amici*, nor is it the experience reflected in the scientific literature. *See, e.g.*, B. Borah et al., "Predictors of Adherence Among Alzheimer's Disease Patients Receiving Oral Therapy," 26 Current Med. Research & Op. 1957 (2010) (42% of Alzheimer's patients studied were noncompliant with their medical prescriptions); *see also* JA __ (Polivka-West Hrg. at 627) ("[T]he resistance to care, the agitation, the resistance to medication especially is well known and recognized.").[4] The unfortunate reality is that in many cases, the administration of medicine to an Alzheimer's patient is a struggle, and in those cases it matters if the caregiver has to fight the battle twice per day or only once. *See*, *e.g.*, JA __ (Dr. Kohrman Hrg. at 738).[5] Moreover, the well-documented phenomenon of sundowning means that evening pill administration is even more likely to present difficulties, difficulties

[4] Dr. Lah himself concedes that "treatment regimens with fewer doses are easier to follow than regimes with more doses." JA __ (Dr. Lah Hrg. at 95).

[5] Dr. Rovner explains the situation thus: "Many people with [Alzheimer's Disease] do not understand their medications or their medical conditions. Their impaired memory makes taking medications an unfamiliar task each day, one that requires the caregiver to explain, every day, what the medications are, what they are for, and why the person needs to take them. Patients often fail to comprehend these otherwise simple explanations and may become suspicious and resistant. This establishes an adversarial situation that caregivers must negotiate with skill and empathy. The scenario repeats itself every day, sometimes multiple times a day, depending on the drug regimen. This is why a simplified medication regimen is helpful. Once-a-day Namenda XR meets this need." JA __ (Dr. Rovner Decl. ¶ 41).

that can be avoided with once-daily formulations such as Namenda XR. *Id.*; JA __ (Polivka-West Hrg. at 627); JA __ (Dr. Rovner Decl. ¶ 42). In any event, even crediting Dr. Lah's characterization of his own clinical experience, that experience, in the respectful opinion of the *amici*, is not representative of this patient population.

We are also concerned that the district court may have oversimplified the issue of pill burden to the point of error. There is a wide variation in the care-giving situations for Alzheimer's patients, with some cared for by spouses, others by their children, family members, or paid caregivers, and still others in various forms of institutional care. And there is wide variation within each of those categories. It is highly misleading, given this extremely-variable reality on the ground, to reduce the issue to nine pills versus eight dispensed in a nursing home setting as the district court does. *See* SA-55 (P.I. Op. ¶ 83) ("[T]he average patient in a long-term care facility takes nine pills per day. . . . Thus, a patient that switches from Namenda IR to Namenda XR might go from nine pills a day to eight pills a day[.]"). Most Alzheimer's patients are not, however, in institutional care and may not take nine pills per day, and hence the inferences that the court attempts to draw from its hypothesized example are simply not valid for most Alzheimer's patients. In some cases, for example, a family member might be able to stop by the patient's home in the morning but not at night, with the result that

many or all evening doses are missed. A patient may "sundown" and refuse to take medication at night, and a caregiver may simply capitulate, resulting in missed doses. We know with certainty that on average more pills means more error, even for a professional caregiver. Given this reality and variability, the place to turn for answers is the scientific literature, not a single, conjectural scenario involving nine pills versus eight in a long-term care facility. That literature is very clear about the benefits of reduced pill burden and once-daily administration (as the district court itself acknowledges earlier in its order).

The notion that once-daily Namenda administration provides insignificant or marginal benefit improperly discounts the importance of pill burden and adherence for patients with dementia; contradicts the relevant scientific literature; and, in the opinion of the *amici*, is not medically sound.

II. THE DISTRICT COURT WRONGLY CONCLUDED THAT SWITCHING TO XR RISKS HARM TO PATIENTS

The record below is also conclusive, in the view of the *amici*, that switching from the IR to the XR formulation of Namenda does not harm patients. The district court's theory of harm is unclear from the order, but logically must be either that some difference between the Namenda IR and XR formulations is harmful to patients or that switching itself is disruptive of their routines and therefore detrimental. *See* SA-55 (P.I. Op. ¶ 85) ("For some patients (and their

physicians), the benefits of the change to Namenda XR are outweighed by the risks of changing the medical routine of a highly vulnerable patient."); SA-55-56 (P.I. Op. ¶ 85) ("'For Alzheimer's patients, stability is key: this is a very vulnerable group of patients. Any small change in medication raises the risk of an adverse effect.'"). But neither concept finds support in the scientific literature, the clinical studies of XR, or the clinical experience reflected in the record; on the contrary, both propositions are directly refuted.

Specifically, the FDA reviewed the XR clinical trials, compiling two years of data:

> The safety and efficacy of Namenda ® XR was demonstrated from one pivotal phase III placebo-controlled study (Study MEM-MD-50) and three open-label safety studies (MEM-MD-51, MEM-MD-54, and MEM-MD-82). Efficacy was demonstrated in Study MEM-MD-50 . . . . MD-51 was an open label one year safety study that included both treatment naïve patients (Group 1) and patients who were receiving memantine IR 10-milligram [twice daily] (Group 2); the group 2 results suggest that patients who receive memantine IR 10-milligram [twice daily] can safely switch to memantine ER 28 milligrams/day with good tolerability.

FDA Pharmaceutics Review at 73; *see also id.* at 4-7, 71-72.[6] The FDA thus found, based on clinical evidence, that there is no harm in switching from IR to XR. And based on that finding, the FDA approved the label instruction for XR allowing a patient to switch from IR to XR the next day. *See* FDA-Approved Package Insert for Namenda XR at 2.

[6] Pace Decl. Ex. 15, attached to Actavis' Motion to Stay (Dkt.41-6).

The other evidence of record fully supports the FDA's conclusion that switching is safe:

- "I've transitioned dozens of patients from twice a day [Namenda] to once a day. I have not had any problems in any patients. The patients accept it. The caregivers are happy to be able to give medication once a day instead of twice a day. Efficacy has been maintained. And, surprisingly, since the XR actually gives a higher average blood level throughout the day of medication, there has been no notable increase or change in the incidence of side effects or in the side effect profile moving from the twice-a-day to the once-a-day preparation. It's quite simple to make the change." JA __ (Dr. Kohrman Hrg. at 738-739);
- "There have been no . . . problems [in switching from Namenda IR to Namenda XR]." JA __ (Dr. Reisberg Hrg. at 725); *see also id.* at 724 ("I have not observed such [adverse] effects [from switching], and the literature does not support those effects.");
- "[T]here have been four studies done looking at Namenda XR. One of these studies was presented to the academic community in a poster authored by Dr. M[e]yers. And this study specifically had one group in it in which patients were switched from Namenda IR to Namenda XR, we call it. Some people refer to this as the switching study or switchability study. And in this study, the science shows that there was no significant or notable increase in the incidence of adverse effects or in the safety profile of Namenda XR when patients were switched from IR to XR." JA __ (Dr. Kohrman Hrg. at 741).

If something about the Namenda XR formulation caused adverse effects, or if twice-daily pill administration were a vital routine, whose disruption would undermine adherence to the detriment of patients, we would expect to see empirical evidence of that—*i.e.*, some indication of harm to patients who switched. Not only do we not see that evidence, we see contrary evidence showing no

adverse impact whatsoever on these patients.[7] The district court has thus elevated conjecture over cogent, and contrary, scientific evidence to hypothesize harm where none exists.[8]

The notion that twice-daily pill administration is an important routine to be preserved is fallacious. It would mean never changing the regimen to lower pill burden. But reduction of pill burden is universally regarded as beneficial (albeit one of potentially many treatment goals), *see* JA __ (Polivka-West Hrg. at 636) ("[A]ny time you can limit the number of [pills] and reach the ultimate level of medication that is desired . . . you have a responsibility to do that."); JA __ (Dr. Reisberg Hrg. at 727) ("[O]nce daily formulations of medications, if they're equally effective, are to be preferred to multiple daily medications. One of my jobs as a physician is to minimize medications . . . ."), and Namenda XR is the last of several important improvements of this kind in Alzheimer's medications. JA __ (Dr. Kohrman Hrg. at 739) ("[N]ow with the introduction of Namenda XR since

[7] Indeed, even though the XR formulation is a higher dose, the studies show no increase in adverse events.

[8] Similarly, there is no evidence of any difficulty in switching a patient back to Namenda IR from the XR formulation, and indeed the existing evidence is that the so-called reverse commute has no adverse effect on patients. *See* JA __ (Dr. Kohrman Hrg. at 742) ("They didn't experience any side effects. There would be none expected since there was really no change in the side effect profile . . . ."); JA __ (Dr. Reisberg Hrg. at 726) ("[T]here were no problems in switching [our] patients back to the IR. . . . So by no problems, I mean no adverse events and also no other problems.").

the middle of 2013 . . . all of the Alzheimer's preparations are available in once-a-day dosing[.]").

The district court nevertheless concluded that, "[f]or some patients (and their physicians), the benefits of the change to Namenda XR are outweighed by the risks of changing the medical routine of a highly vulnerable patient." SA-55 (P.I. Op. ¶ 85). This conclusion rests on a confusion. There may be aspects of an Alzheimer's patients routine whose disruption may be upsetting or detrimental: the substitution of a new caregiver or relocation to a new facility, for example. Elimination of an unnecessary extra pill administration, however, does not fall within that category. The reason is that patients in the moderate to severe category of dementia are unlikely even to be aware of the change. *See* JA __ (Dr. Kohrman Dep. at 203) ("[I]n the moderate to severe stage[,] [t]hey don't know it's medication time, and this is the kind of patient who, if you're in a room with them and they ask you, you know, what day is it, you tell them, they're likely to ask you the same thing one minute later. They don't remember what just happened. So disruption, taking a medicine once a day versus taking a medicine two times a day, that's—that doesn't happen."); *id.* at 204 ("[P]atients at the moderate to severe stage of disease, at which point Namenda is indicated according to its prescribing label . . . are not patients that would be disturbed by taking—by not taking an extra pill. If anything, the converse. These are patients that can be disturbed by having

to take pills."); JA __ (Polivka-West Hrg. at 628) ("[T]he benefits of going from twice a day to once a day far outweigh any concern that there may be change in the routine.").

The district court relied heavily (in substance, exclusively) on the testimony of Dr. Lah in reaching its conclusion. Dr. Lah states that he is "loath" to change the regimen of a patient "if they're doing well on the medication," JA __ (Dr. Lah Hrg. at 58), and that, because Alzheimer's patients are a vulnerable group, "[a]ny small change in medication" including switching from Namenda IR to XR "raises the risk of an adverse effect," that might even "require him or her to be moved to a care facility," JA __ (Dr. Lah Decl. ¶ 24). These assertions not only lack evidentiary support, they contradict the clear evidence of record that switching from IR to XR results in no adverse effect on patients. Indeed, in his testimony, Dr. Lah conceded having no scientific or evidentiary basis to assert that switching creates a risk of harm. *See* JA __ (Dr. Lah Dep. at 279) ("I have no foundation or basis on which to conclude that [patients] either will or will not have greater or lesser tolerability or that an individual patient will have greater adverse effects going to XR from IR. It's a potential concern, not a known concern."). He also admitted having little to no experience in actually switching patients from IR to

XR in his practice.[9] JA __ (Dr. Lah Hrg. at 94); JA __ (Dr. Lah Dep. at 219-220). In sum, the linchpin of the district court's harm finding is testimony that, by the witness's own admission, lacks any "foundation or basis." *See* SA-55-56 (P.I. Op. ¶¶ 85-86).

The *amici* strongly disagree with the notion that changing a routine to *reduce* pill burden is somehow detrimental to patients either in general or in the specific context of Namenda IR and XR. It is not detrimental, as the FDA correctly found and as the practitioners and authorities of record amply show.

III. THE DISTRICT COURT WRONGLY CONCLUDED THAT CLINICIANS WOULD BE UNWILLING OR UNABLE TO CONTINUE PATIENTS ON IR

The district court's third mistaken conclusion, in the view of the *amici*, is that without the injunction physicians who wish to continue a patient on Namenda IR will be unable or unwilling to write that prescription, between now and July 2015, if Forest changes Namenda IR distribution to the specialty mail order pharmacy Foundation Care, or thereafter, when generic IR becomes available. The

[9] One must also be careful about what, precisely, "doing well" means in the context of an Alzheimer's patient. The nature of the condition is that the patient's cognitive faculties are on a downward trajectory (though not always a linear one). The trajectory might flatten or plateau on a better drug or on the same drug with better delivery, *e.g.*, Namenda XR. A policy of never trying to improve the prescription regimen because a patient appears to be benefiting from the drug and is not suffering side effects is not one with which *amici* would agree.

basis for this conclusion appears to be that having to fax a one-page prescription-like form to a specialty pharmacy will impede physicians who wish to prescribe Namenda IR; that having to sign above a statement of medical necessity on the form will preclude physicians from prescribing; and/or that physicians will not opt for the IR generic formulation after July 2015 because they do not take patients' preferences concerning drug cost into consideration.

The *amici* regard each of these propositions as incorrect. They use specialty pharmacies and forms like the one at issue here on a regular basis; the notion that they and other physicians would be dissuaded from writing appropriate prescriptions by this process is dubious. JA __ (Dr. Kohrman Hrg. at 758) ("We talked yesterday about other specialty pharmacies and, you know, drugs that I've prescribed through them. It's not a barrier to prescribing. It's easy to do."); JA __ (Dr. Reisberg Hrg. at 729). Moreover, the *amici* agree with the defendant-appellant's experts below that writing a prescription is already, in effect, a statement of medical necessity, such that the statement on the form presents no additional barrier. *See* JA __ (Dr. Kohrman Hrg. at 745). Finally, the *amici* reject the unsupported notion that doctors do not care about patient cost and do not take it into account in writing prescriptions. The *amici* would not hesitate to prescribe generic Namenda IR for this reason, and they have full confidence that other physicians would do likewise if they considered it appropriate in light of cost or

other factors.[10] "Physicians care about costs of medications and about cost to our patients." JA __ (Dr. Kohrman Hrg. at 757); Dr. Reisberg Hrg. at 731); *accord*, JA __ (Dr. Lah Hrg. at 101).

IV. THE DISTRICT COURT'S ORDER DOES NOT APPEAR TO HELP OUR PATIENTS AND MAY HARM THEM IF IT ADVERSELY AFFECTS THE AVAILABILITY OF XR FORMULATIONS OR OTHER IMPROVED MEDICATIONS

The United States relies fundamentally on brand-name drug companies to fund innovation in medicine. This is not to slight or minimize the importance of academic and government-funded research. But the latter carry only a small proportion of the financial burden. Indeed, if we were to compare the societal cost of a disease like Alzheimer's to the amount of public, academic, and charitable funding devoted to research and development, we would find this funding woefully inadequate to the task. As a society, for good or ill, we have adopted a market-based approach: we address the public health issues of the day, in large measure, by incentivizing private industry to seek and develop the needed therapies, cures, and solutions.

It follows that by disrupting the existing system of incentives—embodied, in important part, in the patent law—we risk jamming the gears that generate therapeutic progress. The *amici* are not economists or experts on the

[10] It is highly likely that the affected insurance companies, HMOs, and similar entities will, at a minimum, raise cost as a consideration with the physicians.

pharmaceutical industry, but they know where new drugs come from and are concerned that reducing the incentive of drug companies to improve their formulations will reduce options and stifle innovations that may help their patients.

The *amici* and other care providers benefit from incremental improvements of existing drugs, improvements that, while not amounting to a cure or even a watershed change in therapy, nonetheless reflect hard-won and meaningful progress for patient care. The XR formulation of Namenda represents the last of three such improvements of the drugs presently prescribed for Alzheimer's Disease, from multiple-daily to once-daily formulations. Together, these refinements improve the care and management of Alzheimer's patients, in many cases allowing for all medications to be taken at one time during the day—a significant advantage, as discussed above, given the unique challenges that confront this population.

Forest/Actavis recently won approval for another such improvement, Namzaric, which combines the extended-release formulation of memantine, *i.e.*, Namenda XR, with donepezil, a widely-used cholinesterase inhibitor ("CI"), in a single, once-daily pill. The *amici* understand that the district court's order may impede or delay Forest's ability to make Namzaric available because it must now compete with Namenda IR for limited production and validation infrastructure. If this proves to be the case, it will be an unfortunate and detrimental outcome for

patients and caregivers, reducing their options and maintaining an unnecessarily high pill burden.

By contrast, the *amici* see little upside for their patients in the district court's order. Although its rationale appears to be ensuring the availability of Namenda IR for the next six months, Namenda IR is already available and, according to Forest's public statements, would remain available during that period without the injunction. Without the district court's order, the *amici* and other clinicians are free to prescribe Namenda IR to their patients if they consider it appropriate, using a perfectly-reasonable, low-hassle process that is familiar and routine in clinical practice and results in direct delivery of the medication to the patients and their caregivers.

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION, TYPEFACE REQUIREMENTS, AND TYPE STYLE REQUIREMENTS

1. This brief complies with the type-volume limitation of Fed. R. App. P. 32(a)(7)(B) because it contains 5,303 words, excluding the parts of the brief exempted by Fed. R. App. 32(a)(7)(B)(iii).

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Dated: January 15, 2015

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CERTIFICATE OF SERVICE

I hereby certify that on this 15th day of January, 2015, a true and correct copy of the foregoing Brief was served upon all counsel of record via ECF pursuant to Local Rule 25.1(h).

I certify that six hard copies of the foregoing Brief were sent today via Federal Express to:

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U.S. Court of Appeals for the Second Circuit
Thurgood Marshall United States Courthouse
40 Foley Square
New York, NY 10007

Dated: January 15, 2015

By: s/ H. Bradford Glassman

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