Depression and Bipolar Support Alliance

Overview

For people living with bipolar disorder, the past 25 years have seen anemic progress in the development of meaningful new treatments. People electing such treatment are frustrated by, and losing hope of a pharmacologic solution. As a nationally recognized and balanced voice for people with the lived experience of bipolar disorder, the Depression and Bipolar Support Alliance (DBSA) has built bridges among numerous diverse constituencies serving as a connector to stakeholders, including individuals with the lived experience, family members, clinicians, researchers, and the biopharmaceutical industry. DBSA believes that meaningful innovation in treatment will be aided by understanding, first and foremost, how those receiving treatment define success, rather than simply relying upon the assessments of clinicians and researchers. Further, DBSA believes that every person deserves the opportunity not just to survive, but to thrive. To do that, we need to ensure true wellness as the end goal for people living with bipolar disorder. It is from this perspective that DBSA is uniquely positioned to comment on the ICER Vesicular Monoamine Transporter 2 Inhibitors for Tardive Dyskinesia Draft Scope Document.

Tardive Dyskinesia (TD) is an involuntary movement disorder caused by dopamine receptor blocking drugs used to treat a number of psychiatric conditions, including bipolar disorder and major depressive disorder. As more and more patients are treated with dopamine receptor blocking drugs, more patients are at risk of TD, even with newer drugs. TD treatments to date have focused solely on the involuntary movement themselves. Although we are encouraged by the FDA approval of the first treatment for TD earlier this year, we recognize this provides an opportunity to look ahead to assessing the broader impacts of these conditions, and treating not just the symptoms, but the entire patient. DBSA looks forward to working with ICER to help bring the patient perspective to their deliberations.

Individuals think in terms of their overall health and in terms of how the different components of their health play out among the communities they are participating in—where they live, work, play, and pray. The goals for clinical success must focus on providing a pathway to a life well-lived as defined by the individual. Because this is not often the defined objective for clinicians or researchers, the potential exists for the patient's definition of success to be obscured. A holistic approach is necessary to support wellness. The idea of wellness cannot be embraced without considering the whole health of the individual and, untreated or under-treated bipolar disorder can disproportionately negatively affect an individual's whole health.

The comorbidities associated with bipolar disorder are not insignificant and the effect treating bipolar disorder has on the positive outcomes of comorbid conditions is well known. Untreated or under-treated bipolar disorder decreases adherence to clinical regimens, is associated with less healthy lifestyles around diet, exercise and smoking, and is associated with higher mortality. TD can lead to treatment non-adherence and associated problems, even though TD may not resolve even if the offending medication is discontinued.

Assessing the effectiveness of TD inhibitors cannot be untangled from the effects on whole health to treating bipolar disorder, and it cannot be overlooked that many patients living with bipolar disorder do not take medications as prescribed. Any assessment must consider the role TD plays in these decisions.

The stated aim of the project is to "evaluate the comparative clinical effectiveness and economic impacts." But to effectively assess effectiveness of VMAT2 inhibitors, understanding TD and other underlying causes for

abandonment of pharmacologic interventions and what outcomes patients seek from an effective treatment of bipolar disorder must be taken into consideration. The table below illustrates some of the whole-health considerations patients evaluate when assessing the risks and benefits of one particular treatment over another for treating bipolar disorder.

Whole-Health Considerations
Patients want options to choose what is best for them.

Symptom Relief	depressed mood • feelings of guilt • work and activities •retardation/psychomotor • agitation • genital • hypochondriasis • loss of weight • insight • anxiety: somatic and psychic • somatic: general and gastrointestinal • suicide • insomnia: early/late/middle
Side-Effect Minimization	psychiatric • cardiovascular • endocrine • metabolic • neurological (including tardive dyskinesia)• gastrointestinal • dermatologic • respiratory • musculoskeletal • immunologic
Well-Being Gains	autonomy • interest in activities • environmental mastery • personal growth • purpose in life • positive relations with others • self-acceptance • cheerful mood • calm and relaxed • wake-up rested

What's important to patients?
While symptom relief and side-effect management are already typically captured by the clinical trials, a data gap remains in measuring well-being and it is not addressed in this project assessment. We believe that in order for patients to make informed treatment decisions regarding their unique and complex mental health conditions, limiting information to clinical effectiveness is inadequate. The social isolation, stigma, and functional impacts of TD are harder to measure, but are critically important, as they are both themselves a barrier to wellness and contribute to other such barriers.

Further, while today's clinical and drug development environment remains focused on symptom relief, patients have reported this is not what is most important to them. Patients are seeking interventions that help them function in life rather than alleviate their symptoms. Examples include:

- relief from bad decision-making
- ability to work and earn an income
- getting better sleep

Given the wide variety of medications, the different side-effects associated with them, and the fact that symptom relief is not the greatest benefit a patient is seeking, it is not surprising that patients don't often take the medication as prescribed. When evaluating the effectiveness of VMAT2 inhibitors, understanding if patients have stopped taking medication to treat bipolar disorder because of well-being concerns must be considered.

Recommendations

Depression and Bipolar Support Alliance

Adapting assessment scope to include tools that measure wellness outcomes as defined by people with TD has the potential to greatly improve treatment outcomes for individuals living with bipolar disorder. Therefore, DBSA recommends that the model structure be expanded to include bipolar disorder.

A next logical step is the inclusion of measureable well-being outcomes that are sensitive, patient-centric, and captured in real-time. It should be noted that the current assessment scope does include patient-reported outcomes, but with a delayed reporting cycle, this methodology opens the possibility that the participant's mood has changed between the time of the event and the reporting—creating the potential for inaccurate data capture. It is understandable that in the time-frame of an existing clinical study these longer-term outcomes may be difficult to effectively capture, but ICER should be encouraged to continue real-world outcomes studies to better understand these potential benefits.

Several scales such as the Ryff Scale of Psychological Well-Being, the Sheehan Disability Scale, and the WHO- 5 Well-Being Index measure well-being domains. The focus of these scales is improvement in environmental autonomy from an interpersonal relationship and work/school perspective. Because these scales do not focus on the reduction of a given symptom, their use of global questions more accurately reflects each individual's unique experience living with TD and whether or not the treatment is bringing improvement to their lives. ICER should consider these scales as additional measures in long-term studies. Additionally, technology exists today to capture well-being in real time. Many wellness trackers including one provided by DBSA (which includes WHO-5 Well-Being Index domains) enable real-time collection and documentation of an individual's mood and sense of well-being.

New treatments for TD are welcome, but more work is needed to fully understand the impact of these treatments on patients, beyond their reduction in involuntary movements. The lack of objective and quantifiable measurement tools in the clinical trial model necessitates additional acceptable measures to get a complete picture of a medicine's potential risks and benefits for people with lived experience. Including well-being patient reported outcomes has potential to move beyond the clinical trial model to capture what is truly important to patients. This model takes into consideration the lost opportunity cost when drugs for Tardive Dyskinesia are not available and would enhance ICER's leadership position in understanding the cost-effectiveness of a health care intervention.

Sincerely,

Allen Doederlein

Allen Doederlein
President, Depression and Bipolar Support Alliance

May 12, 2017

Institute for Clinical and Economic Review
Two Liberty Square,
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Re: Tardive Dyskinesia Open Input Period

Dear Members of the New England Comparative Effectiveness Public Advisory Council:
Mental Health America (MHA) applauds the Institute for Clinical and Economic Review (ICER) for its thoughtful analysis in the *Draft Background and Scope* of the tardive dyskinesia topic, and for inviting the patient perspective throughout. We wanted to take this opportunity to highlight some additional considerations for the simulation models focusing on comparative value.

Mental Health America (MHA) – founded in 1909 – is the nation's leading community-based nonprofit dedicated to addressing the needs of those living with mental illness and to promoting the overall mental health of all Americans. Our work is driven by our commitment to promote mental health as a critical part of overall wellness, including prevention services for all, early identification and intervention for those at risk, and integrated care and treatment for those who need it, with recovery as the goal. A key part of this includes helping consumers navigate the side-effects of medication, including tardive dyskinesia. MHA recently conducted a series of focus groups around the country with individuals living with tardive dyskinesia. We witnessed first-hand the devastation wrought by this debilitating disorder. An overwhelming theme that emerged was the dire need for more effective treatments.

From our experience with individuals living with tardive dyskinesia, we urge ICER to include three areas of value to patients and reciprocal reductions in costs to the health care system:

1. **Increased tolerability of current antipsychotic regimen.** If the tardive dyskinesia side-effects can be successfully treated, then individuals may find their current antipsychotic regimen more tolerable, potentially improving adherence and, as a result, effectiveness.[1] Thus, in some proportion of cases, individuals will receive not only the benefit of the tardive dyskinesia treatment, but also an additional benefit from their antipsychotic medications, potentially offering better outcomes for the underlying mental health condition. The possibility of better outcomes for the underlying condition should be reflected in the model for the probabilities of gains in quality of life and functioning, as well as associated health care cost reductions associated with successful condition management.

[1] Masand PS, Narasimhan M. Improving adherence to antipsychotic pharmacotherapy. Current Clinical Pharmacology. 2006 Jan 1;1(1):47-56.

2. **Improved management of co-morbid conditions.** Individuals living with tardive dyskinesia frequently have co-morbid conditions, such as diabetes or heart disease.[2] In some instances, the gains in functioning associated with treating tardive dyskinesia may improve the individual's management of co-morbid conditions. For example, if tardive dyskinesia led to social isolation and depression, treatment may enhance an individual's success in making lifestyle changes or adhering to insulin or other treatment regimens. Social isolation itself is also highly associated with morbidity and mortality from a variety of non-mental health conditions.[3] The benefits to both improved quality of life and reduced health care costs for co-morbidities in these instances should be integrated into the simulation.

3. **Decreased need for support from public health care payers.** Tardive dyskinesia may substantially inhibit an individual's ability to maintain or advance in competitive employment. Because of this, treatment of tardive dyskinesia may enable some individuals to find and maintain employment. Th employment they find may make the difference between using Medicaid or Medicare (through SSDI), or being able to access commercial health insurance. It is likely that a large proportion of individuals living with tardive dyskinesia currently access health care through Medicaid and/or Medicare. ICER should offer a separate simulation for public payers that takes into account the savings to the government that would accrue in instances where individuals no longer require safety net coverage when they enroll in commercial health insurance.

MHA thanks ICER for its attention to this topic, and hopes to be a resource throughout the process. For additional information, please do not hesitate to contact us.

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[2] Jones DR, Macias C, Barreira PJ, Fisher WH, Hargreaves WA, Harding CM. Prevalence, severity, and co-occurrence of chronic physical health problems of persons with serious mental illness. Psychiatric Services. 2004 Nov;55(11):1250-7.
[3] Steptoe A, Shankar A, Demakakos P, Wardle J. Social isolation, loneliness, and all-cause mortality in older men and women. Proceedings of the National Academy of Sciences. 2013 Apr 9;110(15):5797-801.

National Alliance on Mental Illness

Comments to the Institute for Clinical and Economic Review (ICER) Draft Scope for Effectiveness and Value Review for Tardive Dyskinesia Treatment

May 26, 2017

On behalf of the National Alliance on Mental Illness (NAMI), please find the attached comments on ICER's background and scope proposal for its planned effectiveness and value review of available treatments for tardive dyskinesia. As the nation's largest organization representing people living with serious mental illness, NAMI is grateful for this opportunity to share our views.

As the ICER draft background and scope document accurately notes, tardive dyskinesia (TD) is a serious neurological movement disorder with a delayed onset that is often related to prolonged use of antipsychotic medications that block the dopamine receptor. While TD is most often associated with prolonged use of older antipsychotic agents (commonly identified as "first-generation" antipsychotics), TD has been known to occur with newer antipsychotic drugs (commonly identified as "second-generation" or "atypical" antipsychotics).

Individuals living with serious mental illness that experience TD face enormous challenges and most cope with symptoms that can create enormous social stigma. The involuntary movements associated with TD can be localized or diffuse and can result in physical and psychological impairment. TD can manifest as a hyperkinetic, involuntary movement disorder in the mouth and face region, which can present as lip smacking or pursing, chewing, facial grimacing, and tongue movements inside the mouth or tongue popping out. TD can also impact an individual's arms, legs and torso and result in repetitive foot tapping, finger movements, dystonic postures of the neck and trunk that can include rocking and rotatory movements. Some people living with TD may not be aware of these involuntary movements, especially when involving the face, and thus the condition can result in enormous stigmatization.

While there is already significant stigma associated with mental illness, co-morbid TD can compound this stigma dramatically. While there is no "cure" for TD, there are existing treatments and promising new treatments on the horizon. As the ICER draft notes, the FDA recently approved a new treatment for TD and is currently reviewing a second submission for approval.

These recent developments – a new on-label treatment approved by the FDA and another on the near-term horizon – is a very exciting development for individuals living with TD. The possibility of an effective therapy to treat the disorder and manage symptoms would be of enormous value to patients. These clinical advances hold the promise of allowing individuals with TD the opportunity to fully participate in their community. As noted above, the symptoms of TD can lead directly to social isolation, the inability to interact with the public in settings such as employment, shopping, dining, leisure or activities such as riding the bus or walking in a public park or mall. In short, the ability to effectively manage the symptoms of TD can dramatically improve the lives of people living with this condition.

Any review of these new interventions MUST take into account and provide significant weight to the value of allowing someone living with TD to pursue opportunities such as employment, community integration, developing interpersonal relationships, interacting with strangers and other aspects of daily life that those that have never experienced TD take for granted.

While NAMI will concede that such quality of life measures are not easy to quantify, they are what really matter to people living with this condition – the fact that their symptoms too often prevent them from engaging in employment or participating in community life free of an unwanted public stare from a child or unknowing stranger. NAMI is disappointed that this proposed scope fails to adequately take into account the personal burden that persons living with TD must bear every day.

NAMI would like to offer the following comments on the draft background and scope of the ICER review:

1. By limiting the focus to clinical effectiveness and economic impact, the ICER review fails to consider the social impacts of TD, its impact on family caregivers and how TD contributes to other medical co-morbidities.

As noted above, NAMI is disappointed that the proposal scope excludes consideration of social impacts associated with TD. Involuntary muscle movements in the mouth and face region, facial grimacing, lip smacking and other symptoms associated with TD carry enormous social stigma. This, in turn, leads to further social isolation and exacerbation of the negative symptoms associated with psychotic disorders such as schizophrenia. Likewise, in the case of mood disorders such as bipolar disorder, the social isolation resulting from TD can further exacerbate depression and lack of self-worth. Finally, this social isolation is often associated with a sedentary lifestyle, a poor diet and other factors that result in co-morbid chronic medical conditions associated with serious mental illness.

NAMI strongly recommends that ICER integrate into the scope of this review consideration of the significant value that individuals living with TD place on the potential to effectively manage their symptoms and improve their prospects for employment, community integration and interpersonal relationships.

2. Limiting the scope of the review to schizophrenia is problematic.

In NAMI's view, this fails to capture the full breadth of the population impacted by TD. Over the years, the use of first generation antipsychotics was not limited to schizophrenia and included other conditions such as schizoaffective disorder, bipolar disorder, borderline personality disorder and major depression with psychosis. In fact, there is evidence indicating higher prevalence of TD in mood disorders and schizoaffective disorder. Further, with second generation antipsychotics, on-label indications for use of these medications has expanded significantly in recent years to include new uses and new populations of patients. Excluding these diagnoses will likely limit the utility of this ICER review for these patient populations. NAMI would recommend that, at minimum, ICER expand the scope of this review to other diagnoses for which first generation antipsychotics have been prescribed.

3. In describing "stopping/changing" of antipsychotic treatment, the proposed ICER scope document fails to consider the risk associated with such an approach and the lack of evidence supporting its effectiveness.

In real life clinical practice, reducing, replacing, or removing antipsychotic treatment can jeopardize recovery and stability for people living with a serious mental illness. Interrupting treatment also increases the risk of an episode of acute psychosis, mania and suicidal ideation. Further it fails to recognize the importance of choice and autonomy for individual patience and

the value of shared decision making between prescriber and patient. Our NAMI 800 number Helpline takes hundreds of thousands of call each year to assist people with mental illness in finding treatment. Through this experience, we are well aware of the challenge people face in finding the right medication for their particular circumstance. This has led us to take strong position against public policies that promote switching of medications.

NAMI strongly recommends that ICER not include this as an acceptable treatment option for TD as part of this review.

4. The subpopulations of individuals living with TD described in the scope document are problematic and lack evidence to support such distinctions.

While TD symptoms can impact multiple musculoskeletal systems (e.g. oral-facial v. arms-feet), there is little, if any, evidence on the burden by body region. Likewise, there are not yet recognized clinical standards for defining distinctions between moderate or severe TD. NAMI would recommend that ICER take into account quality of life and other measures of social integration alongside the frequency amplitude of symptoms.

5. NAMI is concerned that the scope of review specifically includes an off-label intervention for TD for which there is limited evidence in existing clinical treatment guidelines

A broad range of effective off-label treatments currently exist for mental illness supported by peer reviewed clinical treatment guidelines published by recognized specialty societies. However, with respect to TD, the last task force convened by the American Psychiatric Association was in 1992. Since that time, TD has been recognized in schizophrenia management guidelines on a number of occasions, most recently in 2009. While the scope document does cite treatment guidelines from both the APA and the American Academy of Neurology (AAN), it fails to note that the AAN guidelines declared that there are no treatments for TD that achieved a "Level A" designation for strength of evidence. In short, the off-label treatment included in this proposed scope lacks strong evidence and creates the unwarranted conclusion that there are effective off-label treatments currently available to treat TD. By contrast, the emerging on-label treatment for TD have been through the rigorous process of FDA approval and are supported by separate randomized controlled trials, the highest level of evidentiary reliability.

Many in NAMI's consumer and family membership continue to struggle everyday with TD. For too many of them, outdated off-label treatment has not offered them relief from this disabling and enormously stigmatizing condition. The promise of two near therapies that offer some hope of improvement and recovery is long overdue. NAMI urges ICER to ensure that the design of this proposed review does not lead to results that limit access to potentially promising therapies.

Thank you for considering NAMI's comments on the important issue of treatments for tardive dyskinesia.

Sincerely,

Mary Giliberti, J.D.
Executive Director

Neurocrine BIOSCIENCES

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May 26, 2017

Dear ICER review team for tardive dyskinesia,

We appreciate the interactive teleconference last week and we have a preliminary response to your *Draft Background and Scope document released 5/8/2017*. Clearly, there are several concepts and assumptions which require further discussion. The highlights below include additional citations or information that should be supportive for your efforts.

Throughout the document, it is stated that the foundation of the ICER analysis and the development of either cost effectiveness (CE) thresholds will be based on data regarding patients with tardive dyskinesia and underlying schizophrenia. We are including information (slides) from a recent IMS study showing that schizophrenia is but a small percentage of patients being prescribed antipsychotics and, as such, reflect only a fraction of patients at risk for - or afflicted with - Tardive Dyskinesia (TD). Schizophrenia patients do not adequately reflect the target population for medications to treat TD. For a comprehensive and applicable CE analysis, all patients suffering from TD need to be considered along with their underlying psychiatric and medical conditions. It would be remiss to use only the limited information that is available and ignore the potential impact on the other TD populations (eg, bipolar disorder, major depressive disorder). To assist you with some additional disease-burden data (from varied patient groups with TD) we are attaching a survey recently conducted by the Depression and Bipolar Support Alliance (DBSA) patient advocacy group.

Additionally, basing a model on only schizophrenia patient data would diminish the informative nature of burden and utilities output because of the differential impact of TD on patients with underlying disease states. For example, high-functioning patients suffering from depression or bipolar disorder should be considered in a different context re: employment and productivity than a patient with chronic paranoid schizophrenia living a group home.

We also suggest that you not include tetrabenazine (TBZ) as a comparator for TD. Tetrabenazine is not approved for TD, it has not been adequately studied for TD and, perhaps most importantly, it carries safety and pharmacologic liabilities which limit its use in TD. The inappropriateness of comparisons between tetrabenazine and valbenazine in the treatment of TD are supported by Grigoriadis et al. (JPET 2017) and a systematic literature review recently presented by Neurocrine at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual Meeting [attached].

Another facet of your analysis that should be revised is the concept of severity and analysis of effectiveness or cost effectiveness by severity. As you will likely discover in your research, there is no medically accepted threshold for identifying the severity of TD across diverse presentations and clinically distinct underlying disease states. The abnormal involuntary movement scale (AIMS) is a useful tool in both clinical trials and clinical practice, but its utilization for these different purposes may affect how the AIMS is scored and interpreted. Excessive variability in AIMS scoring can be constrained in clinical trials, as exemplified by the recent studies of valbenazine (NBI-98854) in adults with TD (KINECT 2 [NCT01733121], KINECT 3 [NCT02274558]. In these studies, blinded central raters viewed standardized video recordings of subjects being administered the AIMS throughout the trials and evaluated these

videos using a scoring protocol. The central raters were blinded to whether the subjects were receiving active treatment or placebo. Moreover, the raters did not know which study visit that they were viewing since the sequence of the videos was scrambled. Finally, the valbenazine studies included well-defined anchors for each AIMS item to minimize inter-rater variability, and all AIMS scoring required a consensus between two central raters who watched the videos together.

In clinical practice, however, AIMS scoring may reflect physician experience and bias, which could vary considerably among providers. For example, AIMS scoring and the associated description of an individual patient's "TD severity" may depend on the overall range of severity with which a physician has experience. Scoring may also be affected by other factors, such as inadequate or outdated training. Therefore, AIMS ratings conducted in the controlled setting of a clinical trial (e.g., based on standardized video recordings and a scoring protocol) may not have exact numeric correspondence with physician-based ratings conducted in a non-research context (e.g., based on face-to-face interaction with the patient). For example, a mood disorder subject who receives an AIMS item score of 3 for the tongue (only affected region) would have an AIMS total score of 3. This score might be considered "low" in a clinical trial in which the efficacy of an anti-dyskinetic agent is being evaluated within a group of subjects based on a reduction in the AIMS mean total score. In a clinical setting, however, the same patient may appear to have a quite disabling tongue dyskinesia with considerable disruption to social and work activities and be judged by a practicing physician to have "moderate" or even "severe" TD. Thus, while the AIMS does have face validity (for item scores), it does not have ideal clinimetric properties such as linearity (for the total score).

Finally, before the approval of Ingrezza, the recommendations based on limited evidence of effectiveness increased the risk of worsening psychiatric status (eg, tetrabenazine) or worsening TD or other dyskinesia symptoms (eg, benztropine). Additionally, lack of efficacy of treating TD can lead to poor psychiatric treatment compliance or even self-discontinuation which again leads to decompensation and very poor or expensive outcomes.

AIMS and CGI-TD- As stated previously, the AIMS is a measure of movement amplitude and frequency (in the viewpoint of the evaluator) the only purpose of the "score" is to evaluate change from a previous measure. The Clinical Global Impression of change-TD is much more of a subjective evaluation of the reviewer of "improvement". It is very challenging to create or convey a correlation or relationship with the AIMs and CGI-TD because the determination of "improvement" can depend on the number of body region affected by TD as well as the amount of change in each of the affected areas. For example it would make sense that a 3 point AIMs change (lowering) in an individual with only a single body region affected could experience a complete elimination of symptoms and thus be evaluated as "very improved". Conversely an individual with 5 body regions affected could experience a 5 point AIMs change (lowering) but each region is minimally effected by treatment could be evaluated as somewhat improved or even neutral. For this reason, trying to correlate AIIMs and CGI-TD could be very misleading. In our trials the AIMs was administered by the investigator, but scored by blinded central raters. Whereas the CGI-TD was administered and scored by the investigator which may confound the correlation between these two very different measures

PGIC- The Patient Global Impression of Change (PGIC) scale may be a helpful instrument for patient-reported assessment of treatment impact of valbenazine in tardive dyskinesia. In the Phase 2b KINECT 2 study [O'Brien 2015] a statistically significant difference was demonstrated between the valbenazine and placebo groups after 6 weeks of treatment with mean scores of 2.2 vs. 2.9 ($p=0.0011$) respectively. Per the pre-specified response threshold, 57.8% of valbenazine subjects vs. 31.8% of placebo subjects achieved a score of 1 (very much improved) or 2 (much improved). It is worth noting, as

stated previously, that patients with schizophrenia and schizoaffective disorder have limited insight into their underlying psychiatric disorders and drug-related adverse events so this patient-reported outcome may have limited application in clinical practice.

Health related QOL- This will become a very important facet to evaluate when the data, especially underlying mental illness specific data) become more available with symptom burden studies (REKinect for example).

Treatment related adverse events- Adverse events and overall tolerability are important concepts when assessing the clinical utility of tardive dyskinesia treatments. Given the relative pharmacologies of available agents and those in development, rationale exists to believe there may be differential profiles in the risk for harm. In both the 6-week double-blind, placebo-controlled and 48-week double-blind treatment phases valbenazine exhibited low incidence rates of adverse events considering the subjects' numerous comorbidities and concomitant medications. In the clinical development program no clinically relevant changes were observed in lab values, physical exams, vital signs, or electrocardiogram measurements. It is of interest that 1) a variety of psychiatric scales (PANSS, YMRS, MADRS, CDSS, C-SSRS) demonstrated maintenance of psychiatric stability over long-term studies and 2) valbenazine does NOT have a boxed warning for increased risk of depression or suicidality as does other VMAT2 inhibitor medications.

Discontinuation due to adverse events- To understand the true "value" of a TD treatment the entire treatment continuum and risk of discontinuation of therapies need to be evaluated. Most guidelines state step 1 would be to eliminate the offending agent. For many of the mental illness populations this isn't a viable option. In fact, the risk is decompensation due to missing psychiatric agents. The next suggested step is to switch to a different psychiatric treatment (less offending antipsychotic) this also creates an element of risk for AEs and for reduced psychiatric compliance and possible decompensation. Finally, before the approval of Ingrezza, were recommendations for treatments with very limited evidence of effectiveness or even increased risk of worsening psychiatric stability (tetrabenazine) or worsening TD or other dyskinesia symptoms (benztropine). Additionally, the lack of efficacy of treating TD can lead to poor psychiatric treatment compliance or even self-discontinuation which again leads to decompensation and very poor/expensive outcomes.

Costs and Cost effectiveness – As you are likely aware, there are few data available to formulate burden dis-utilities and thus effectiveness utilities. As we/ICER work to develop a CE threshold, we can interact and share data as they becomes available. With regards to costs/budget impact I am including the language from our AMCP format dossier and the budget impact model (BIM)." The economic impact of INGREZZA® (valbenazine) capsules is presented in section 4.0 Economic Value and Modeling Report. The model describes the budget impact of adoption of INGREZZA® (valbenazine) capsules in a hypothetical health plan of 1,000,000 commercially insured enrollees. Base case results show INGREZZA® (valbenazine) capsules increases costs by $0.17 per member per month over a three-year time horizon. Overall, these findings imply that providing INGREZZA® (valbenazine) capsules in this setting will have a relatively modest budget impact on a healthcare plan.

Sincerely,

Chris O'Brien, MD, FAAN
Chief Medical Officer

Teva Pharmaceuticals
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May 26, 2017

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review

RE: TEVA's Response to ICER's Background and Scope Document entitled "Vesicular Monoamine Transporter 2 Inhibitors for Tardive Dyskinesia: Effectiveness and Value" (dated May 8, 2017)

Dear ICER Evaluation Team members,

TEVA appreciates an opportunity to provide comments on the ICER's evaluation of VMAT-2 class inhibitors for the treatment of TD. TEVA's comments are included below.

- **Heterogeneity within TD population**: It is important to note the diversity and number of sub-populations within the TD population. TD commonly precipitates from use of dopamine receptor blocking agents (DBRAs). Since DRBAs are administered to patients for a variety of reasons, this leads the TD patient population to being heterogeneous. Examples of underlying conditions necessitating DRBAs could include schizophrenia, major depressive disorder, bipolar disorder, as well as non-psychiatric disorders (e.g., GI motility). These underlying conditions vary greatly in disutility and mortality (Salmon et al 2012). It will be important to take into account the heterogeneity of the TD patient population in any economic analysis.

- **Significance of antipsychotic therapy modification implications in the economic evaluation**: ICER has appropriately noted in the scoping document that for psychiatrists and neurologists who treat patients with anti-psychotic agents and manage their side effects, therapy for tardive dyskinesia has primarily focused on changing the underlying psychiatric agent to manage symptoms. Published studies of anti-psychotic therapy dose-reduction strategies to minimize the risk of developing extrapyramidal symptoms including TD, have generally reported significant risks of psychotic exacerbation and relapse (Davis et al. 1994; Wang et al 2010). It can be reasonably expected that with the availability of FDA approved therapies, the use of underlying psychiatric agent modification as a treatment strategy would be significantly reduced and as a result a significant reduction in the risk of psychotic exacerbations and relapses should occur. It will be important to include the expected clinical and economic benefits of being able to maintain effective antipsychotic therapy in the economic evaluation of VMAT-2 inhibitors in the management of TD. This will be in line with the ICER's note in the scoping document that emphasizes the need to capture " ... the full range of benefits and harms.." in the evaluation.

- **Use of anticipated real-world compliance and persistence rates with VMAT-2 inhibitors in the evaluation**: ICER has noted that Tetrabenazine has been used off-label for TD. ICER has also noted its limited usefulness due to its clinical profile including side effects. These factors and its impact on therapy outcomes need to be considered in any economic modeling of its use in the management of TD. In addition, as the majority of patients with TD have underlying psychiatric conditions, the rate of adherence to medications in this patient population is low (Kane et al 2013). This should also be considered in the economic models of any medication use in this patient population.

- **Importance of ensuring robust cross-trial comparison between different VMAT-2 inhibitors**: ICER has noted that Network Meta-Analysis (NMA) or qualitative comparison and high quality observational studies may be included in the evaluation. While the highlighted approaches are valuable, it would be important to ensure that such approaches are used appropriately after taking into consideration study design variabilities and quality.

- **Appropriateness of including TBZ in the evaluation**: ICER has stated that components of their evaluation will include all VMAT-2 inhibitors. While it is intuitive to include all VMAT-2 inhibitors, including TBZ within the economic analysis may not reflect real world practice. Currently, TBZ is not FDA approved for use within TD and based on our understanding of real-world treatment patterns in TD, TBZ use in TD patients has been low (< 1%).

- **Estimating and including appropriate TD population size that will be treated with VMAT-2 inhibitors**: ICER has noted that estimating the TD population size will be a factor in calculating the budget impact of new TD treatments. It would be of importance to ensure that the estimation of the size of the TD population that would receive treatment includes real-world factors impacting therapy utilization. These factors include, but are not limited to, severity of TD, physician adoption of new treatment options, patient access to treatment, mis-diagnosis/ under-diagnosis of TD patients, etc. Though robust information on some of these factors may not be readily available, best efforts to reflect real world treatment rates will help the analysis be more meaningful for health care decision makers.

Sincerely,
Sanjay Gandhi, PhD
Sr. Director, Global Health Economics and Outcomes Research
Global Medical Affairs
on behalf of Teva Pharmaceuticals

References

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