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Comments to CMS regarding selected drugs for price negotiations (round 3)

March 1, 2026

Pursuant to the Inflation Reduction Act (IRA) of 2022 (P.L. 117-169) and in direct response to a call for information from the Centers for Medicare & Medicaid Services (CMS), Public Citizen's Health Research Group offered the following five comments regarding drugs that are the subject of price negotiations in the context of the Medicare program. These comments aim to give CMS information that it can use to negotiation fair prices for these and related drugs moving forward. The comments, reproduced verbatim below, were posted at the dedicated CMS submission portal on March 1, 2026.

Comment listing:

Comment 1. onabotulinumtoxinA (Botox, Botox Cosmetic)

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Response to question 46a*.On which indication(s) of the selected drug would you like to provide input?*

OnabotulinumtoxinA temporarily blocks the nerve signals that cause muscles to contract; therefore, it is used for several therapeutic and cosmetic indications.[1]

The responses below focus on four common therapeutic indications for onabotulinumtoxinA that have been approved by the Food and Drug Administration (FDA): (1) Treatment of cervical dystonia (also known as spasmodic torticollis), which is a disorder that causes abnormal, uncontrollable and often painful abnormal head placement, in adult patients; (2) prevention of headaches related to chronic migraine in adult patients; (3) treatment of spasticity of lower-limb muscles in patients 2 years of age or older (including those with cerebral palsy); and (4) treatment of strabismus, a common condition associated with either constant or intermittent deviation of the ocular alignment (one eye is turned in a direction that is different from the other eye, including inward [esotropia] or outward [exotropia] deviation), in patients 12 years of age or older.

Public Citizen's Health Research Group does not address any cosmetic indications of onabotulinumtoxinA because they are not covered under Medicare and Medicaid. Moreover, we advise against the use of any botulinum toxin drug for cosmetic purposes because their potential risk of systemic spread outweighs any potential temporary benefit of smoothing skin wrinkles or fine lines.[2]

Response to question 47. *What medications would you consider to be potential therapeutic alternatives for the selected drug for each indication?*

The therapeutic alternatives for onabotulinumtoxinA and other botulinum toxin drugs vary depending on the indication. For cervical dystonia, two common treatment alternatives are physical therapy (to strengthen or stretch the neck muscles) and oral anticholinergic drugs (such as trihexyphenidyl [generics only]), which can help with relaxing the muscles by interfering with signal transmission mediated by acetylcholine and its receptors.

For the chronic migraine prophylaxis, alternative treatments include lifestyle modifications, biobehavioral therapy (such as cognitive behavioral therapy, biofeedback, and mindfulness-based therapies), and certain drugs (such as the antiepileptic drugs divalproex [Depakote and generics]).[3] It is not clear how antiepileptic drugs prevent migraine, but they appear to decrease brain hyperexcitability associated with migraine attacks in susceptible individuals.

For lower-limb spasticity in children with cerebral palsy, alternative treatments include physiotherapy, orthosis, and serial casting, which provide consistent ways to improve joint range of motion and reduce muscle stiffness.

For strabismus, alternative treatments include conservative therapy (lens therapy, orthoptic exercises, or prisms) or strabismus surgery.

***Response to question 48c**. By indication and for each alternative drug versus the drug of focus, identify and briefly describe evidence on the comparative effectiveness. Include descriptions of the methods.*

CERVICAL DYSTONIA

To the best of our knowledge, onabotulinumtoxinA has been compared with placebo only in clinical trials assessing the drug's effectiveness for treating cervical dystonia. A Cochrane review that examined evidence from double-blind, parallel randomized controlled trials (RCTs) comparing the effectiveness of botulinum toxin drugs with daily use of anticholinergics in treating cervical dystonia identified one trial.[4] The trial compared the effectiveness of botulinum toxin type A drug abobotulinumtoxinA (Dysport), which works in a similar manner to onabotulinumtoxinA, with the effectiveness of oral anticholinergic drug trihexyphenidyl in 66 participants with cervical dystonia who never received botulinum toxin type A drugs before. AbobotulinumtoxinA reduced cervical dystonia severity by an average of 2.5 points (95% confidence interval [CI] 0.68 to 4.32) on the severity subscale (which ranges from zero to 35 points) of the Toronto Western Spasmodic Torticollis Rating Scale 12 weeks after injection, compared with daily treatment with trihexyphenidyl. However, the researchers characterized this evidence as of "very low-certainty" and found no information supporting a dose-response relationship for botulinum toxin type A drugs. The reviewers concluded, "[D]ue to limitations in the study methods and size of the study, we have very little confidence in the results."

CHRONIC MIGRAINE

To the best of our knowledge, onabotulinumtoxinA has been compared with placebo only in clinical trials assessing the drug's effectiveness for chronic migraine prophylaxis. The drug label reports that two RCTs found that after 24 weeks of follow-up, two-injection cycles of onabotulinumtoxinA reduced the frequency of headache from baseline in treated adult subjects by 1.4 and 2.3 days per 28 days in the first and second trials, respectively, compared with placebo.

Evidence from a Cochrane review of several placebo-controlled RCTs involving botulinum toxin type A drugs found that, at best, these drugs may reduce the number of migraine days by 3.1 (95% CI -4.7 to -1.4) only per month in chronic migraine participants.[5] After removing data from small trials, the reduction was two days (95% CI -2.8 to -1.1) only, an effect that the researchers characterized as being of "moderate quality." Therefore, they concluded, "[I]t is unclear if this improvement was large enough to make a meaningful difference to [participants'] lives. More work is needed to show whether botulinum toxin is better than oral treatments… that prevent migraine." The researchers also noted that the evidence for botulinum toxin drugs for patients with occasional (episodic) migraine was uncertain.

STRABISMUS

A 2023 Cochrane review of RCTs sought to compare the effectiveness of botulinum toxin drugs with either conservative therapy (such as orthoptic exercises, prisms, or lens therapy) or strabismus surgery in participants with strabismus.[6] Of four identified RCTs involving a total of 242 participants (adults with esotropia or exotropia and children with either acquired esotropia or infantile esotropia), none examined comparator conservative treatments (such as lens therapy, orthoptic exercises, or prisms). Instead, all the trials compared the effectiveness of botulinum toxin drugs with strabismus surgery and showed that participants treated with the surgery may be more likely to improve or correct strabismus. However, due to the low quality of the trials, the Cochrane researchers concluded that "[it] remains unclear whether botulinum toxin may be an alternative to strabismus surgery as an independent treatment modality among certain types of strabismus."

LOWER-LIMB SPASTICITY IN CHILDREN WITH CEREBAL PALSY

The FDA approved the use of onabotulinumtoxinA for the treatment of spasticity in pediatric patients in 2019. Since the 1990s, however, the drug has been approved in this patient population in Europe and has been used off label for this indication in the United States. Therefore, there are several studies about the use of this drug in this setting.

A 2019 Cochrane review examined 31 RCTs that enrolled a total of 1,508 children (aged from birth to 19 years) who were injected with either a botulinum toxin type A drug in the lower-limb muscles or received other inventions: physiotherapy or usual care (14 studies), placebo (12 studies), serial casting (4 studies), and orthoses (1 study).[7] Of those, 19 studies involved onabotulinumtoxinA and another three did not describe the toxin type, but onabotulinumtoxinA was most likely the intervention drug, based on the year and dose, according to the Cochrane researchers.

Compared with usual care or physiotherapy, there was very low evidence showing that receiving botulinum toxin type A drugs have improved outcomes (walking/gait pattern, joint range of motion, satisfaction with outcome of treatment, and muscle spasms) in children with cerebral palsy. In addition, children who were injected with these drugs had modest improvements only in their measures of function (assessed using the Gross Motor Function Measure among others).

There was low to moderate evidence that botulinum toxin type A injections had similar benefits to plaster casts below the knee in terms of improving walking and joint motion and relieving muscle spasm. Moreover, there was very low evidence that botulinum toxin type A drugs provided better results in terms of joint range of motion compared with a type of splinting.

Compared with those receiving placebo, children receiving botulinum toxin type A injections had short- and medium-term improvements in their gait scores. However, the treatment did not improve short-term functional outcomes. At best, by medium-term follow-up, there was only a small improvement in function.

The Cochrane researchers concluded that there is "limited evidence that, compared to placebo or regular care, [botulinum toxin type A] improves walking, joint motion, satisfaction with the outcome of treatment, and muscle spasticity in children with [cerebral palsy]."

Response to question 49a. *Summarize evidence regarding patient experiences with the drug in question and its alternatives (adverse events can be included)?*

Although RCTs supporting the approval of onabotulinumtoxinA and other botulinum toxin drugs are supposed to provide critical evidence regarding these products, they are not a good source of uncommon adverse events. This is because these trials were primarily designed and powered to assess the efficacy of these drugs.[8] Therefore, the reporting of safety outcomes tended to be less detailed in these trials, which limited the amount of data that could be gleaned from them. In addition, several of these trials involved passive monitoring of safety outcomes (i.e., adverse events were only recorded if patients voluntarily reported them) instead of active monitoring (i.e., specifically prompting or instructing patients to report safety outcomes).

Moreover, systematic reviews by the Cochrane Collaboration point out that the available RCTs of botulinum toxin drugs were predominantly industry-funded — representing a "high risk of bias" — and that they included "an enriched population with a higher probability of benefiting from this therapy," [9,10] in the sense that these trials excluded patients with poor responses to botulinum toxin treatment. Authors of these reviews characterized the short-term safety evidence from these trials as "low" or "moderate" and cautioned about a lack of evidence for drawing definitive conclusions regarding the optimal treatment intervals and doses of botulinum toxin drugs, because most available evidence from RCTs evaluated the effect of a single botulinum toxin drug treatment session. Meanwhile, most serious adverse events from botulinum toxin drugs are derived from case reports and studies that used data from spontaneous reporting systems.[11]

Nonetheless, there is evidence showing that patients who receive onabotulinumtoxinA or other botulinum toxin drugs are at an increased risk of experiencing adverse events, including dysphagia, neck weakness, and diffuse weakness or tiredness. These adverse events can be serious and are consistent with systemic spread of the toxin, which can cause iatrogenic botulism. Some have argued that the extent of this risk is unclear or may be limited to injections of high doses of botulinum toxin drugs. However, published post-marketing evidence and a primary analysis conducted by Public Citizen's Health Research Group using data from the FDA's Adverse Event Reporting System (FAERS), a database that contains voluntary reports of drug-related adverse events, shows that even when used at recommended doses, either in initial or repeated treatment, both cosmetic and therapeutic botulinum toxin drugs are associated with systemic iatrogenic botulism and related symptoms in some patients.

Our FAERS analysis identified 5,414 reports with serious outcomes (such as death, life-threatening events, hospitalization, or disability) in which a botulinum toxin drug was the only primary suspect. These reports were received by the FDA from January 1989 through March 2021. Of those, 121 (2%) reports specified botulism as an adverse reaction; 89 involved therapeutic uses of botulinum-toxin drugs and 32 involved cosmetic uses. Several of the 121 botulism reports involved botulinum-toxin doses that were within the recommended dose range

for the specified uses. For example, seven of 27 botulism reports involving Botox Cosmetic indicated that the injected doses ranged from 10 to 30 units. In addition, five of the 66 botulism reports involving therapeutic uses of Botox indicated that the injected doses were 50 or fewer units (the maximum recommended dose ranges from 100 to 400 units).

We also found that 2,817 (52%) of the 5,414 serious reports included signs or symptoms that are suggestive of iatrogenic botulism, consistent with the effect of botulinum-toxin drugs. We grouped these signs or symptoms into six categories: (1) those involving the bladder, (2) those involving muscle weakness or paralysis in the extremities, (3) those involving the eyes, (4) those involving the oropharynx (the area in the back of the mouth and upper throat), (5) those involving breathing, and (6) those involving certain abnormal sensations. Many of these reports involved small doses of botulinum-toxin drugs.

Most likely, our analysis greatly underestimated the true extent of serious adverse effects associated with botulinum-toxin drugs — including those of iatrogenic botulism and its suggestive signs or symptoms — due to the voluntary reporting of adverse events to the FAERS database. For example, a systematic review estimated that only 6% of the adverse events of drugs are reported to spontaneous reporting systems, such as the FAERS database.[12]

Instead of declaring the potential risk of systemic iatrogenic botulism and related symptoms explicitly, the current labels of botulinum toxin drugs water down and obscure this serious risk by using a less serious term: distant spread of toxin. These labels also limit the need for administering botulinum antitoxin to the context of excessive dosing, accidental injection or oral ingestion of these products.

Therefore, in 2023 we petitioned the FDA to require the manufacturers of botulinum toxin drugs to make it clear that, even when used at recommended doses, either in initial or subsequent (repeated) treatment, these drugs are associated with systemic iatrogenic botulism and related symptoms.[13] We also asked the agency to make it clear that cases of systemic iatrogenic botulism associated with recommended doses of botulinum toxin drugs may require prompt administration of botulinum antitoxin to avoid disease progression and serious outcomes, including temporary muscle paralysis, hospitalization, and death.

Importantly, there is a growing body of research showing an increased risk of sustained muscle atrophy (sarcopenia) and fibrofatty tissue replacement in areas injected by botulinum toxin drugs.[14] Several imaging studies in animal models and humans demonstrate that intramuscular injection of standard therapeutic doses of these drugs impact muscles in ways that go beyond temporary denervation.[15,16] This includes acute muscle atrophy (identified by reductions in muscle cross-sectional area), reduced volume of contractile elements, increased collagen-based tissue, and other changes in muscle tissue structures.

Response to question 49b Describe any specific subpopulations that are of interest regarding the use of the drug in question. Summarize the evidence supporting the unique treatment of each patient subpopulation. Elderly and disabled populations are of particular interest.

See evidence from our response above regarding lower-limb spasticity in children with cerebral palsy.

Response to question 51. What other information or evidence do you think CMS should consider in the evaluation of the selected drug?

There is no strong evidence from RCTs supporting a net benefit of onabotulinumtoxinA compared with alternative treatments for the four indications discussed above.

The effect of botulinum toxin drugs is limited by their temporary action. Therefore, repeated injections of these drugs are needed. However, most of the available evidence from RCTs does not examine multiple, repeated cycles of botulinum toxin injection. Therefore, some researchers have concluded that there is no evidence from RCTs to make definitive conclusions regarding the optimal treatment intervals and doses of these drugs, their duration of effect, or their impact on quality of life.[17]

Furthermore, patients and clinicians should consider the risk of systemic iatrogenic botulism and atrophy in the injected muscles before embarking on any treatment with botulinum toxin drugs.

Therefore, Public Citizen's Health Research Group urges CMS to keep all this information in mind during price negotiations with the manufacturers of onabotulinumtoxinA and other botulinum toxin drugs.

REFERENCES

1. AbbVie. Label: onabotulinumtoxinA (Botox) [Internet]. November 2023 [cited 2026 Feb 26]. Available from: https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=33d066a9-34ff-4a1a-b38b-d10983df3300&type=display.
2. Public Citizen urges FDA to strengthen warning on labeling of BOTOX and related drugs [Internet]. Worst Pills, Best Pills News [Internet]. March 2024 [cited 2026 Feb 26]. Available from: https://www.worstpills.org/newsletters/view/1586.
3. Ailani J, Burch RC, Robbins MS. The American Headache Society consensus statement: update on integrating new migraine treatments into clinical practice. Headache. 2021;61(7):1021-1039. doi:10.1111/head.14153.
4. Rodrigues FB, Duarte GS, Castelão M, et al. Botulinum toxin type A versus anticholinergics for cervical dystonia (review). Cochrane Database Syst Rev. 2021;4(4):CD004312. doi:10.1002/14651858.CD004312.pub3.
5. Herd CP, Tomlinson CL, Rick C, et al. Botulinum toxins for the prevention of migraine in adults. Cochrane Database Syst Rev. 2018;2018(6). doi:10.1002/14651858.CD011616.pub2.
6. Bort-Martí AR, Rowe FJ, Sifre LR, et al. Botulinum toxin for the treatment of strabismus (review). Cochrane Database Syst Rev. 2023;3(3):CD006499. doi:10.1002/14651858.CD006499.pub5.
7. Blumetti FC, Belloti JC, Tamaoki MJS, Pinto JA. Botulinum toxin type A in the treatment of lower limb spasticity in children with cerebral palsy. Cochrane Database Syst Rev. 2019;10(10):CD001408. doi:10.1002/14651858.CD001408.pub2.

8. Gostimir M, Liou V, Yoon MK. Safety of botulinum toxin A injections for facial rejuvenation: A meta-analysis of 9,669 patients. Ophthalmic Plast Reconstr Surg. 2023;39(1):13-25. doi:10.1097/IOP.0000000000002169.
9. Duarte GS, Rodrigues FB, Marques RE, et al. Botulinum toxin type A therapy for blepharospasm. Cochrane Database Syst Rev. 2020;11(11):CD004900. doi:10.1002/14651858.CD004900.pub3.
10. Rodrigues FB, Duarte GS, Marques RE, et al. Botulinum toxin type A therapy for cervical dystonia. Cochrane Database Syst Rev. 2020;11(11):CD003633. doi:10.1002/14651858.CD003633.pub4.
11. Yiannakopoulou E. Serious and long-term adverse events associated with the therapeutic and cosmetic use of botulinum toxin. Pharmacology. 2015;95(1-2):65-69. doi:10.1159/000370245.
12. Hazell L, Shakir SAW. Under-reporting of adverse drug reactions: A systematic review. Drug Saf. 2006;29(5):385-396. doi:10.2165/00002018-200629050-00003.
13. Public Citizen. Petition to the FDA to strengthen safety warning for Botox and related drugs and remove misleading claims from Botox/Botox Cosmetic labeling [Internet]. December 12, 2023 [cited 2026 Feb 26]. Available from: https://www.citizen.org/article/petition-to-the-fda-to-strengthen-safety-warning-for-botox-and-related-drugs-and-remove-misleading-claims-from-botox-botox-cosmetic-labeling.
14. Lennon N, Church C, Salazar-Torres JJ, et al. Changes in motor function in a child with cerebral palsy following multiple botulinum toxin injections: A case report. Children. 2025;12(6):761. doi:10.3390/children12060761.
15. Ibid.
16. Multani I, Manji J, Tang MJ, et al. Sarcopenia, cerebral palsy, and botulinum toxin type A. JBJS Rev. 2019;7(8):e4. doi:10.2106/JBJS.RVW.18.00153.
17. Rodrigues FB, Duarte GS, Marques RE, et al. Botulinum toxin type A therapy for cervical dystonia. Cochrane Database Syst Rev. 2020;11(11):CD003633. doi:10.1002/14651858.CD003633.pub4.

Comment 2. brexpiprazole (REXULTI)

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Response to question 46a*.On which indication(s) of the selected drug would you like to provide input?*

- Treatment of agitation associated with dementia due to Alzheimer's disease
- Treatment of schizophrenia in adults and pediatric patients ages 13 years and older
- Use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) in adults

Response to question 47. *What medications would you consider to be potential therapeutic alternatives for the selected drug for each indication?*

- Treatment of schizophrenia in adults and pediatric patients ages 13 years and older→ aripiprazole (Abilify) [see response to Question 48c below for details]
- Use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) in adults→ aripiprazole (Abilify) [see response to Question 48c below for details]

Response to question 48c*. By indication and for each alternative drug versus the drug of focus, identify and briefly describe evidence on the comparative effectiveness. Include descriptions of the methods.*

Brexpiprazole (REXULTI and generics) is an oral atypical antipsychotic that acts as a partial agonist at dopamine D2 and serotonin 5-HT1A receptors and as an antagonist at serotonin 5-HT2A receptors. [1] The drug was first approved in 2015 to treat schizophrenia, as well as major depressive disorder in conjunction with antidepressants such as fluoxetine (PROZAC and generics). [2]

In May 2023 the Food and Drug Administration (FDA) approved brexpiprazole for the treatment of agitation associated with dementia due to Alzheimer's disease. [3] Public Citizen opposed this approval [4] and subsequently designated brexpiprazole as a "Do Not Use" drug for Alzheimer's disease-associated dementia. [5] Brexpiprazole is the first FDA-approved drug for this condition, and FDA approval was based on five small, short-term trials. For evaluation of efficacy, the FDA used data from three of these trials. Only two trials showed statistically significant clinical improvement in agitation, and only for some of the study participants taking the drug. The improvements were marginal and likely too small to be clinically meaningful. Importantly, all five studies found that brexpiprazole was associated with serious adverse effects; compared with placebo, there was an increased risk of death. [6]

In the three trials evaluated for efficacy, the primary measure was change in the Cohen-Mansfield Agitation Inventory (CMAI) score, which has a range of 29 to 203 points. Two trials showed that treatment with brexpiprazole led to statistically significant improvements in the CMAI score compared with placebo. [7] In one of these trials, 433 adults were randomized to a daily fixed dose of 1 or 2 milligrams (mg) of brexpiprazole or a placebo. After 12 weeks, all groups showed an improvement in CMAI score. However, there was no additional improvement over placebo in the 1-mg brexpiprazole group, and the 2-mg group improved by only 4 points on the CMAI scale as compared to the placebo group. The FDA did not consider this 4-point difference to be "statistically persuasive." [8] In the second trial, 345 adults were randomized to a 2 or 3 mg dose of brexpiprazole or placebo. The difference in the CMAI score between the treatment and placebo groups was approximately 5 points, again raising questions about the clinical relevance of a small improvement. [9]

A 2026 meta-analysis combined the results of four randomized controlled trials that were not evaluated by the FDA. Data were evaluated for about 1,440 people with dementia from Alzheimer's disease. The meta-analysis similarly found a pooled mean difference of –3.94 points on the CMAI scale between the brexpiprazole group and placebo groups (95% CI –6.21 to –1.67).[10] To put this change in CMAI scores in context, a 2024 industry-sponsored analysis determined that a meaningful within-patient change on the CMAI scale likely requires a drop of approximately 20 points (threshold range -15 to -25 points). [11] The observed mean CMAI differences of 4 or 5 points between brexpiprazole and placebo found in the available studies do not establish the meaningful clinical efficacy of brexpiprazole for agitation from Alzheimer's disease.

Brexpiprazole's safety profile raises additional concerns. Among patients with Alzheimer's disease taking brexpiprazole for agitation, approximately 13% will discontinue the drug due to adverse effects. [12] The drug carries a boxed warning for increased mortality in older patients with dementia-related psychosis.[13] In the trials reviewed by the FDA, brexpiprazole was associated with an increased the risk of death and higher rates of adverse events than placebo, such as nasopharyngitis (3% vs. 2%), urinary tract infections (3% vs. 1%), somnolence (3% vs. 1%), and dizziness (3% vs. 2%).[14] As is the case with other antipsychotics, use of brexpiprazole may also cause metabolic changes, including hyperglycemia (20% vs. 9%) and abnormally high triglycerides (18% vs. 5%). [15]

In patients with dementia, antipsychotics as a class are consistently associated with increased mortality. A 2018 meta-analysis including over 380,000 dementia patients found that antipsychotic exposure was linked to substantially increased mortality; the study analyzed the data with three independent methods. The risk of death among antipsychotic users was approximately double that of the control non-user group (HR = 1.93 [1.72-2.22], HR = 2.10 [2.0-

2.2] and HR =2.0 [1.6-2.7]). [16] Although first-generation antipsychotics are considered to have a higher mortality risk than second-generation antipsychotics, the mortality risk of second-generation antipsychotics is still substantial. A literature review of adverse outcomes in older adults with dementia, published in 2023, concluded that atypical antipsychotics, when compared with placebo, increased mortality with an overall number needed to harm (NNH) of 73. [17]

Antipsychotics are also associated with a broad range of serious adverse effects in patients with dementia. A matched cohort study of 173,910 adults with dementia, published in 2024, found increased risks of stroke (HR 1.61, 95% CI 1.52-1.71), venous thromboembolism (HR 1.62, 95% CI 1.46-1.80), myocardial infarction (HR 1.28, 95% CI 1.15-1.42), heart failure (HR 1.27, 95% CI 1.18-1.37), fracture (HR 1.43, 95% CI 1.35-1.52), pneumonia (HR 2.19, 95% CI 2.10-2.28), and acute kidney injury (HR 1.72, 95% CI 1.61-1.84) among antipsychotic users compared with matched non-users. [18] The study found that both first-generation and second-generation antipsychotics were associated with increased risks of adverse outcomes, although risks were higher with first-generation antipsychotics for stroke, heart failure, fracture, pneumonia, and acute kidney injury. [19] The literature review published in 2023 similarly identified elevated risks of pneumonia, cerebrovascular events such as stroke and transient ischemic attack, venous thromboembolism, gait disturbance, and sedation associated with antipsychotic use in dementia. [20] A 2016 systematic review of meta-analyses also reported that the use of antipsychotics among individuals with dementia results in "a greater number of adverse effects when compared with individuals treated with placebo," including cerebrovascular adverse events, sedation, abnormal gait, and extrapyramidal symptoms. [21]

Brexpiprazole is biochemically similar to other "third-generation" (dopamine partial agonist) antipsychotics, especially aripiprazole, but the comparative evidence does not show meaningful advantages that would justify brexpiprazole's cost (a one-month supply of brexpiprazole costs about $1,500, whereas aripiprazole costs $15). [22,23] In a 2020 systematic review and meta-analysis of randomized trials in acute schizophrenia, Kishi and colleagues found that both aripiprazole and brexpiprazole were superior to placebo, but no outcomes differed between aripiprazole and brexpiprazole for short-term efficacy or safety. [24]

Comparative findings in another clinical context — adjunctive treatment for major depressive disorder (MDD) — also suggest only minor differences between brexpiprazole and aripiprazole. A 2023 meta-analysis comparing four atypical antipsychotics used as augmentation therapy found that both aripiprazole and brexpiprazole were more effective than placebo, with effect sizes that were close in magnitude (aripiprazole standard mean difference [SMD] ≈ –0.28 [-0.47 to -0.09] and brexpiprazole SMD ≈ –0.25 [-0.42 to -0.07] for MADRS depressive symptom score change). The meta-analysis also found no significant differences in safety between all four antipsychotic agents included in the study (brexpiprazole, aripiprazole, quetiapine, and olanzapine). [25]

For major depressive disorder, second-generation antipsychotics are adjunctive therapy and should only be used if first-line treatments are not effective. An example of a first-line treatment is antidepressant monotherapy with a selective serotonin reuptake inhibito. [26] If a second-generation antipsychotic is used as adjunctive treatment for depression, The Medical Letter on Drugs and Therapeutics notes that "Aripiprazole…has the most data supporting its efficacy and safety for this indication." [27]

For treatment of schizophrenia, the comparative reviews cited above have consistent findings: brexpiprazole is therapeutically similar to other partial-agonist antipsychotics — especially aripiprazole — with no consistent evidence of superior efficacy and no clear evidence of improved safety or patient acceptance that would justify routine use instead of lower-cost alternatives. Additionally, the evidence favors use of aripiprazole, not brexpiprazole, for adjunctive therapy for major depressive disorder.

REFERENCES

1. Jarrett J, Infante A. Brexpiprazole (Rexulti) for the treatment of agitation associated with Alzheimer disease. American Family Physician. 2024; 110(5): 537–538.
2. Otsuka. Label: brexpiprazole (REXULTI). May 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/205422s014lbl.pdf. Accessed February 25, 2026.
3. FDA approval of brexpiprazole for agitation symptoms associated with dementia due to Alzheimer's disease: A concerning decision. Worst Pills, Best Pills News. August 2023. https://www.worstpills.org/newsletters/view/1546. Accessed February 25, 2026.
4. Public Citizen. Letter to the FDA opposing approval of brexpiprazole for the treatment of agitation associated with Alzheimer's dementia. May 3, 2023. https://www.citizen.org/article/letter-to-the-fda-opposing-approval-of-brexpiprazole-for-the-treatment-of-agitation-associated-with-alzheimers-dementia/. Accessed February 25, 2026.
5. Brexpiprazole: Do Not Use for agitation due to Alzheimer's dementia. Worst Pills, Best Pills News. October 2023. https://www.worstpills.org/newsletters/view/1559. Accessed February 25, 2026.
6. Ibid.
7. Ibid.
8. Ibid.
9. Ibid.
10. Javaid H, Jha A, Cheema U, et al. Dose-dependent efficacy and safety of brexpiprazole in agitation associated with dementia in Alzheimer's disease: A systematic review and meta-analysis. Neurological Sciences. 2026; 47, 208. doi: 10.1007/s10072-025-08649-y.

11. Meunier J, Creel, K, Loubert A, et al. Defining a clinically meaningful within-patient change threshold for the Cohen-Mansfield Agitation Inventory in Alzheimer's dementia. Frontiers in Neurology. 2024; 15, 1379062. doi:10.3389/fneur.2024.1379062.
12. Jarrett J, Infante A. Brexpiprazole (Rexulti) for the treatment of agitation associated with Alzheimer disease. American Family Physician. 2024; 110(5), 537–538.
13. Ibid.
14. Otsuka. Label: brexpiprazole (REXULTI) May 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/205422s014lbl.pdf. Accessed February 23, 2026.
15. Jarrett J, Infante A. Brexpiprazole (Rexulti) for the treatment of agitation associated with Alzheimer disease. American Family Physician. 2024; 110(5), 537–538.
16. Ralph S, Espinet A. Increased all-cause mortality by antipsychotic drugs: updated review and meta-analysis in dementia and general mental health care. Journal of Alzheimer's Disease Reports. 2018; 2:1-26. doi:10.3233/ADR-170042.
17. Rogowska M, Thornton M, Creese B, et al. Implications of adverse outcomes associated with antipsychotics in older patients with dementia: A 2011–2022 update. Drugs & Aging. 2023; 40: 21-32. doi:10.1007/s40266-022-00992-5.
18. Mok P, Carr M, Guthrie B, et al. Multiple adverse outcomes associated with antipsychotic use in people with dementia: Population based matched cohort study. BMJ. 2024; 385, e076268. doi:10.1136/bmj-2023-076268.
19. Ibid.
20. Rogowska M, Thornton M, Creese B, et al. Implications of adverse outcomes associated with antipsychotics in older patients with dementia: A 2011–2022 update. Drugs & Aging. 2023; 40: 21-32. doi:10.1007/s40266-022-00992-5.
21. Tampi R. Tampi D, Balachandran S, et al. Antipsychotic use in dementia: A systematic review of benefits and risks from meta-analyses. Therapeutic Advances in Chronic Disease. 2016; Vol 7(5): 229-245. doi:10.1177/2040622316658463
22. Good Rx.com website: https://www.goodrx.com/rexulti. Accessed February 25, 2026.
23. GoodRx.com website: https://www.goodrx.com/aripiprazole. Accessed February 25, 2026.
24. Kishi T, Ikuta T, Matsuda Y, et al. Aripiprazole vs. brexpiprazole for acute schizophrenia: A systematic review and network meta-analysis. Psychopharmacology. 2020; 237: 1459–1470. doi:10.1007/s00213-020-05472-5.
25. Wang J, Li W, Li M, et al. Comparative efficacy and safety of 4 atypical antipsychotics augmentation treatment for major depressive disorder in adults: A systematic review and network meta-analysis. Medicine. 2023; 102(38), e34670. doi:10.1097/MD.0000000000034670.
26. Nelson C. Unipolar depression in adults: treatment with second-generation antipsychotics. UpToDate. February 2, 2024.
27. Drugs for depression. The Medical Letter on Drugs and Therapeutics. December 11 2023, Vol. 65(1691): 193-200.

Comment 3. abatacept (ORENCIA)

Author: Michael Abrams, M.P.H., Ph.D.

Response to question 46a.*On which indication(s) of the selected drug would you like to provide input?*

- rheumatoid arthritis,
- psoriatic arthritis

Response to question 47. *What medications would you consider to be potential therapeutic alternatives for the selected drug for each indication?*

- methotrexate (conventional)
- certolizumab pegol (TNF inhibitor)
- tofacitinib (JAK inhibitor)

Response to question 48c. *By indication and for each alternative drug versus the drug of focus, identify and briefly describe evidence on the comparative effectiveness. Include descriptions of the methods.*

INTRODUCTION

Three of the drugs subject to price negotiations for this third cycle (2026) are second-line treatments for rheumatoid arthritis (RA), per evidentiary summaries from independent sources including UpToDate, The Medical Letter, Prescrire International and Worst Pills, Best Pills News.[1,2,3,4] These drugs are certolizumab pegol (CIMZIA), abatacept (ORENCIA), and tofacitinib (XELJANZ). They are substitutes for one another, among several other drugs, as treatments for RA and related conditions that are unresponsive to first-line therapies such as methotrexate (JYLAMVO, RASUVO, TREXALL, XATMEP, and generics). Given their concerning risk-benefit profiles, only abatacept is considered for limited use in the treatment of RA and related inflammatory diseases (if first-line therapies fail) by Public Citizen's Worst Pills, Best Pills News; certolizumab pegol and tofacitinib are classified as Do Not Use.[5,6,7]

In addition to methotrexate, initial disease-modifying treatments for RA include hydroxychloroquine (PLAQUENIL, SOVUNA, and generics), sulfasalazine (AZULFIDINE and generics), and leflunomide (ARAVA and generics).[8] Second-line treatments include five different drugs classified as tumor necrosis factor (TNF) inhibitors (for example, (adalimumab [HUMIRA and biosimilars]), two interleukin inhibitors (tocilizumab [ACTMRA and biosimilars] and sarilumab [KEVZARA]), three Janus kinase (JAK) inhibitors (for example, tofacitinib), and two other biologics (rituximab [RITUXAN and biosimilars] and abatacept).

OVERLAPPING INDICATIONS

Biweekly to monthly subcutaneous injections of certolizumab pegol is indicated for difficult-to-treat Crohn's disease, moderate to severe RA in adults, active polyarticular juvenile idiopathic arthritis, adults with psoriatic arthritis, adults with ankylosing spondylitis, adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation, and adults with

moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[9] Public Citizen's Worst Pills, Best Pills News, as recently as 2024, has classified this drug as Do Not Use because it is no better than other drugs for RA and it carries unique risks for complete hair loss, kidney failure, and cardiovascular disease.[10]

Weekly to monthly subcutaneous (with infusion-induction) injections of abatacept is indicated for moderate to severe rheumatoid arthritis in adults, moderate to severe and active polyarticular juvenile arthritis, psoriatic arthritis in individuals 2 years of age or older, and as prophylaxis for acute graft-versus-host disease (in combination with other drugs) that may result from a blood system transplantation (infusion schedule: day before the procedure as well as day 5, day 14, and day 28 after the procedure).[11]

Daily oral tablets of tofacitinib are indicated for adults with moderately to severely active rheumatoid arthritis "who have had an inadequate response or intolerance to one or more TNF blockers," and similarly so for active psoriatic arthritis, ankylosing spondylitis, or moderate to severe ulcerative colitis that was not treatable with TNF inhibitors.[12]

THREE DIFFERENT BIOMECHANISMS

Certolizumab pegol is a TNF blocker because it selectively neutralizes TNF-alpha cytokines, small proteins involved in the inflammation process.[13] Although Public Citizen's Worst Pills, Best Pills News discourages use of this drug, other TNF blockers are deemed appropriate when first-line therapies fail.[14]

Abatacept inhibits the activation of specific T-cells.[15] T-cells, a type of white blood cells, are formed in the bone marrow and then mature in the thymus gland.[16] There are two main types of T-cells: those that directly attack and destroy invading pathogens and tumor cells and "helper" T-cells that otherwise assist in the immune response, including the removal of invaders.

Tofacitinib is one of a class of drugs known as JAK inhibitor.[17] JAKs are enzymes that transmit signals inside of cells related to cytokine or growth factors that influence blood cell formation and immune cell function. Among other functions they influence the transcription of genes, an early step in the making of proteins.

EFFECTIVENESS WITH OR ABSENT METHOTREXATE

Review of the labels for each of the three medications summarized in this comment shows several blinded, randomized clinical studies demonstrating that these drugs all ameliorate the signs and symptoms associated with RA and other inflammatory indications. The effectiveness in treating moderate to severe RA is summarized below for each drug by highlighting pivotal trials that utilized methotrexate and placebo comparison arms:

Certolizumab pegol was tested by comparing RA treatment with either methotrexate plus the drug (n=393) or methotrexate plus placebo (n=199). Participants in this trial were receiving methotrexate for at least 6 months before engaging in randomization and the 52 weeks of treatment and study follow-up. Participants were limited to "incomplete" responders to methotrexate monotherapy.[18] At 52 weeks, standardized American College of Rheumatology criteria[19] improvements of at least 50% (ACR50) were observed in 38% of those given

certolizumab pegol and 8% of those given placebo (difference score=30%, 95% confidence interval [CI]: 24% to 37%). A similar 24-week study that did not include methotrexate showed a lower ACR50 effectiveness difference score from placebo of 19% (CI: 10% to 28%).[20]

Abatacept was tested by comparing RA treatment with either methotrexate plus the drug (n=424) or methotrexate plus placebo (n=214).[21] ACR50 (50% improvement) at 52 weeks was achieved by 48% of the abatacept group and 18% of the placebo group ($p<0.001$). In a small (n=64) and shorter-duration (12-week) study, those who failed to respond to other disease-modifying drugs and who did not receive methotrexate showed ARC50 rates of 16% for abatacept and 6% for placebo, but this difference was not statistically significant.

Tofacitinib was tested by comparing RA treatment with either methotrexate plus the drug (n=321) or methotrexate plus placebo (n=160).[22] ACR50 rates at 24 weeks were 32% for the tofacitinib group and 9% for the placebo group. A smaller (tofacitinib n=243; placebo n=122), shorter-duration (12-week) study of those who first failed to respond to another disease-modifying drug but who continued that therapy during the trial showed ARC50 rates of 31% for the tofacitinib group and 12% for the placebo group (p-values and CIs not reported).

SAFETY

Certolizumab pegol carries a boxed warning (the most serious label-based caution the FDA issues), which alerts prescribers and patients that using this drug increases the risk of serious infections and cancer.[23] Infections might be tuberculosis, sepsis, or other pathogens that can lead to hospitalization or death. Malignancies also could be fatal; lymphoma was evident in three of 2,376 individuals participating in placebo-controlled clinical trials, about twice the rate of the general population. Randomized clinical trial data comparing biweekly certolizumab pegol plus methotrexate (n=640) to placebo plus methotrexate (n=324) show that upper respiratory infection (6% versus 2%, respectively), hypertension (5% versus 2%), back pain (4% versus 1%), nasopharyngitis (5% versus 1%), and rash (3% versus 1%) were all markedly elevated with certolizumab pegol treatment after at least six months of exposure.

Abatacept does not carry a boxed warning.[24] Its label elsewhere notes serious infections as a prominent warning and precaution, especially when used with a TNF antagonist or in patients with a history of recurrent infections. Among the most common adverse effects observed in clinical trials with intravenous abatacept (n=1,955) and placebo (n=989) were headaches (18% versus 13%, respectively), nasopharyngitis (12% versus 9%), and hypertension (7% versus 4%). This clinical trial included 338 participants who were also taking other disease-modifying biologics for RA during the trial.

Tofacitinib carries a boxed warning for infection and cancer risk elevation similar to that assigned to certolizumab pegol.[25] The tofacitinib boxed warning further cautions prescribers and patients that the drug elevates risk of death and adverse cardiovascular events including thrombosis. The label offers point estimates for each of these serious concerns based on a postmarketing open-label clinical trial in RA patients age 50 or older (mean= 61 years). The trial had three treatment arms: high-dose tofacitinib (10 milligrams [mg] twice daily, n=1,456), low-dose tofacitinib (5 mg twice daily; n=1,455), or a TNF blocker (dosed appropriately; n=1,451). Participants had at least one cardiovascular risk factor and they were studied for a median

treatment period of four years. The incidences of all-cause mortality per 100 patient-years of exposure were, respectively, 1.23, 0.88, and 0.69. The incidence rates of malignancies (excluding nonmelanoma skin cancer cases) were 1.91, 1.53, and 0.99 per 100 patient-years. The incidence rates of major adverse cardiovascular events were 1.11, 0.91, and 0.79 per 100 patient-years. The incidences of thrombosis were 0.28, 0.22, and 0.16 per 100 patient-years. Almost all the comparisons of high-dose tofacitinib and TNF blockers showed statistically significant differences. These serious adverse-event rates thus demonstrate dose-response associations with tofacitinib and this drug's higher risk of serious adverse events compared with TNF blockers. Finally, the incidence of serious infection was especially high across all three groups (high-dose tofacitinib=3.65, low-dose tofacitinib=2.95, TNF blockers=2.52, per 100 patient-years) and TNF blocker treatment was less likely to yield a serious infection than tofacitinib.

One other safety signal is notable, although it was statistically evident in only the pivotal trial data among adults being treated for ulcerative colitis.[26] The 52-week randomized, blinded trial compared 10-mg (n=196) and 5-mg (n=198) twice-daily doses of tofacitinib with placebo (n=198) and found that the second most common adverse reaction, after nasopharyngitis, was elevated cholesterol levels, which were evident in 9%, 5%, and 1% of each group, respectively. The definition of elevated cholesterol included the following metabolic indicators: hypercholesterolemia, hyperlipidemia, blood cholesterol increased, dyslipidemia, blood triglycerides increased, low-density lipoprotein increased, low-density lipoprotein abnormal, or lipids increased.

Recent observational studies comparing JAK inhibitors (including tofacitinib), TNF inhibitors (including certolizumab pegol), and abatacept for RA often confirmed some, though not all, of the most serious adverse effects differentially associated with these treatments, and they also offer point estimates of these adverse effects. Using Medicare claims from 2009 to 2019 corresponding to the experiences of 53,001 individuals treated for RA, Jin et al. 2025 estimated that there were no significant differences in malignancies or thromboembolism when directly comparing JAK inhibitors with abatacept or TNF inhibitors with abatacept, but both comparisons show significant JAK inhibitor- or TNF inhibitor-associated elevations in the risk of heart failure.[27] The authors conclude their findings are limited by the study's power, the ambiguity of claims analysis, and residual confounds. They further "emphasize the need for ongoing safety monitoring" for patients being treated with any disease-modifying medication for RA.

A study by Aymon et al. 2025 did not show that JAK inhibitors were associated with more major adverse cardiovascular effects than TNF inhibitors and other disease-modifying RA drugs.[28] However, this study was relatively short in duration (median follow-up of 1.3 years) and thus it identified a relatively small number of cardiovascular adverse effects: 828 events among 52,233 patients and 73,008 treatment courses. Moreover, this study was industry funded and seemed biased towards downplaying the adverse effects of high-dose JAK inhibitors that are evident on related prescribing information and elsewhere.

Shin et al. 2026 used 2009-2020 data from Korea's National Health Insurance database to compare the infection risks of JAK inhibitors (n=4,252) and TNF inhibitors (6,653).[29] They found that any infection (bacterial, viral, fungal, or other) risk was higher in JAK inhibitor users

than in TNF blocker users (1.66 versus 0.87 hospitalized infections per 100 person-years, respectively).

Schaefer et al. 2025 used 2017 to 2020 data from a German registry of patients receiving disease-modifying RA drugs and confirmed that JAK inhibitors (including many prescriptions of tofacitinib) increased the risk of malignancies, as compared with other RA drugs.[30] Among 2,285 JAK inhibitor recipients, there were 88 resulting malignancies (3.9%); among 4,259 other RA drug recipients, there were 135 malignancies (3.2%) (adjusted hazard ratio= 1.4 [95% CI: 1.1-1.8]). These differences became apparent only with follow-up durations of at least 16 months, and patients over the age of 60 years with greater disease activity had increased risk. This work confirmed the results of previous surveillance trials.

SUMMARY

The totality of this comment is that all three of these RA drugs have demonstrated merit as second-line treatments for RA and associated conditions. However, the risk profile for certolizumab pegol and tofacitinib make them drugs to avoid,[31, 32] thus the "willingness to pay" for the Medicare system should be relatively low. Abatacept should be used only when other first-line therapies, including methotrexate, have failed to provide adequate disease modification via a reduction of harmful inflammation. Even abatacept use carries consequential adverse effects that require intensive clinical monitoring and may yield serious morbidity. These factors should negatively influence the price because they lower the overall benefit-to-risk ratio of abatacept, and because there are alternatives for the treatment of RA and related conditions.

REFERENCES

1. Cohen T. Mikuls TR. Initial pharmacologic management of rheumatoid arthritis in adults. UpToDate. June 10, 2025.
2. Drugs for rheumatoid arthritis. Med Lett Drugs Ther. 2021;63(1637):177-184.
3. Rheumatoid arthritis: choice of antirheumatic treatment. Prescrire International (translated). February 2010 Vol. 19. No. 15.
4. Review of the tumor necrosis factor blocker adalimumab (HUMIRA). Worst Pills, Best Pills News. August 2024. https://www.worstpills.org/newsletters/view/1611. Accessed February 263, 2026.
5. New biologic drugs for rheumatoid arthritis: which are safe? Worst Pills, Best Pills News. March 2016. March 2016. https://www.worstpills.org/newsletters/view/1024. Accessed February 27, 2026.
6. Review of the tumor necrosis factor blocker adalimumab (HUMIRA). Worst Pills, Best Pills News. August 2024. https://www.worstpills.org/newsletters/view/1611. Accessed February 27, 2026.
7. Tofacitinib (XELJANZ, XELJANZ ER) for rheumatoid arthritis increases risk of infections. Worst Pills, Best Pills News. February 2023. Newsletters. Accessed February 27, 2026.
8. Drugs for rheumatoid arthritis. Med Lett Drugs Ther. 2021;63(1637):177-184.
9. UCB. Label: certolizumab pegol (CIMZIA). September 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125160s315lbl.pdf. Accessed February 26, 2026.

10. Review of the tumor necrosis factor blocker adalimumab (HUMIRA). Worst Pills, Best Pills News. August 2024. https://www.worstpills.org/newsletters/view/1611. Accessed February 26, 2026.
11. Bristol-Myers Squibb. Label: abatacept (ORENCIA). May 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125118s255lbl.pdf. Accessed February 26, 2026.
12. Pfizer. Label: tofacitinib (XELJANZ). October 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/203214s039,213082s011lbl.pdf. Accessed February 26, 2026.
13. UCB. Label: certolizumab pegol (CIMZIA). September 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125160s315lbl.pdf. Accessed February 26, 2026.
14. Review of the tumor necrosis factor blocker adalimumab (HUMIRA). Worst Pills, Best Pills News. August 2024. https://www.worstpills.org/newsletters/view/1611. Accessed February 26, 2026.
15. Bristol-Myers Squibb. Label: abatacept (ORENCIA). May 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125118s255lbl.pdf. Accessed February 26, 2026.
16. Cleveland Clinic. T cells. January 17, 2023. https://my.clevelandclinic.org/health/body/24630-t-cells. Accessed February 26, 2026.
17. Pfizer. Label: tofacitinib (XELJANZ). October 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/203214s039,213082s011lbl.pdf. Accessed February 26, 2026.
18. UCB. Label: certolizumab pegol (CIMZIA). September 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125160s315lbl.pdf. Accessed February 26, 2026.
19. Statistical Consultancy Team. ACR response criteria in rheumatoid arthritis clinical trials. September 25, 2024. https://www.quanticate.com/blog/acr-response-criteria. Accessed February 26, 2026.
20. UCB. Label: certolizumab pegol (CIMZIA). September 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125160s315lbl.pdf. Accessed February 26, 2026.
21. Bristol-Myers Squibb. Label: abatacept (ORENCIA). May 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125118s255lbl.pdf. Accessed February 26, 2026.
22. Pfizer. Label: tofacitinib (XELJANZ). October 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/203214s039,213082s011lbl.pdf. Accessed February 26, 2025.
23. UCB. Label: certolizumab pegol (CIMZIA). September 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125160s315lbl.pdf. Accessed February 26, 2026.
24. Bristol-Myers Squibb. Label: abatacept (ORENCIA). May 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125118s255lbl.pdf. Accessed February 26, 2026.

25. Pfizer. Label: tofacitinib (XELJANZ). October 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/203214s039,213082s011lbl.pdf. Accessed February 26, 2026.
26. Ibid.
27. Jin Y, Liu J, Desai RJ. Comparative safety of biologic and targeted-synthetic DMARDs in patients with rheumatoid arthritis: A multi-database real-world cohort study. Pharmacoepidemiol Drug Saf. 2025;34(8):e70193. doi:10.1002/pds.70193.
28. Aymon R, Mongin D, Guemara R, et al. Incidence of major adverse cardiovascular events in patients with rheumatoid arthritis treated with JAK inhibitors compared with biologic disease-modifying antirheumatic drugs: data from an international collaboration of registries. Arthritis Rheumatol. 2025;77(9):1194-1204. doi:10.1002/art.43188.
29. Shin A, Choi SR, Pyo JY, et al. Risk of non-bacterial opportunistic infections associated with Janus kinase inhibitors versus tumor necrosis factor inhibitors among rheumatoid arthritis patients: A cohort study. Joint Bone Spine. 2026;93(1):105945. doi:10.1016/j.jbspin.2025.105945.
30. Schaefer M, Purschke A, Zietemann V, et al. Comparative risk of incident malignancies in rheumatoid arthritis patients treated with Janus kinase inhibitors or bDMARDs: observational data from the German RABBIT register. Ann Rheum Dis. 2025;84(11):1779-1790. doi:10.1007/s00011-025-02170-w.
31. Tofacitinib (XELJANZ, XELJANZ ER) for rheumatoid arthritis increases risk of infections. Worst Pills, Best Pills News. February 2023. https://www.worstpills.org/newsletters/view/1518. Accessed February 26, 2026.
32. Review of the tumor necrosis factor blocker adalimumab (HUMIRA). Worst Pills, Best Pills News. August 2024. https://www.worstpills.org/newsletters/view/1611. Accessed February 26, 2026.

Comment 4. certolizumab pegol (CIMZIA)

Author: Michael Abrams, M.P.H., Ph.D.

Response to question 46a. *On which indication(s) of the selected drug would you like to provide input?*

- rheumatoid arthritis
- Crohn's disease
- juvenile idiopathic arthritis
- spondyloarthritis
- plaque psoriasis

Response to question 47. *What medications would you consider to be potential therapeutic alternatives for the selected drug for each indication?*

- methotrexate (conventional)
- abatacept (T&B cell modulator)
- tofacitinib (JAK inhibitor)

Response to question 48c. *By indication and for each alternative drug versus the drug of focus, identify and briefly describe evidence on the comparative effectiveness. Include descriptions of the methods.*

Please see response to this same question for abatacept.

Comment 5. tofacitinib (XELJANZ)

Author: Michael Abrams, M.P.H., Ph.D.

Response to question 46a. *On which indication(s) of the selected drug would you like to provide input?*

- rheumatoid arthritis
- psoriatic arthritis
- ankylosing spondylitis
- ulcerative colitis

Response to question 47. *What medications would you consider to be potential therapeutic alternatives for the selected drug for each indication?*

- methotrexate (conventional)
- abatacept (T&B cell modulator)
- certolizumab pegol (TNF inhibitor)

Response to question 48c*. By indication and for each alternative drug versus the drug of focus, identify and briefly describe evidence on the comparative effectiveness. Include descriptions of the methods.*

Please see response to this same question for abatacept.