CENTENE PHARMACY AND THERAPEUTICS
NEW DRUG REVIEW
3Q17 July – August

BRAND NAME
Xadago®

GENERIC NAME
Safinamide

MANUFACTURER
Newron Pharmaceuticals SpA – holds license; granted approval.
US WorldMeds, LLC – exclusive licensee and distributor in the U.S.

DATE OF APPROVAL
March 21, 2017

PRODUCT LAUNCH DATE
July 2017

REVIEW TYPE
☒ Review type 1 (RT1): New Drug Review
Full review of new chemical or biologic agents

☐ Review type 2 (RT2): New Indication Review
Abbreviated review of new dosage forms of existing agents that are approved for a new indication or use

☐ Review type 3 (RT3): Expedited CMS Protected Class Drug Review
Expedited abbreviated review of Centers for Medicare & Medicaid Services protected class drugs (anticonvulsants, antidepressants, antineoplastic, antipsychotics, antiretrovirals, and immunosuppressants)

☐ Review type 5 (RT5): Abbreviated Reviews for Intravenous Chemotherapy Agents
Abbreviated review for intravenous chemotherapy agents which are usually covered under the medical benefit

FDA APPROVED INDICATION[1]
Xadago is indicated as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "off" episodes.

Limitations of use: Xadago has not been shown to be effective as monotherapy for the treatment of PD.

CENTENE PHARMACY AND THERAPEUTICS
NEW DRUG REVIEW
3Q17 July – August

OFF-LABEL USES
Not applicable

CLINICAL EFFICACY
The efficacy of Xadago was demonstrated in two pivotal double-blind, placebo-controlled, multi-national 24-week studies. The primary outcome in the two studies was change from baseline in self-reported total daily "ON" Time without troublesome dyskinesia. The secondary outcome in both studies was self-reported "OFF" Time during the diary period and reduction in Uniform Parkinson's Disease Rating Scale (UPDRS) Part III (motor examination). Patients were eligible if they had a diagnosis of PD with off time >1.5 hours per day and were stabilized on oral levodopa for ≥ 4 weeks.[2,3]

Borgohain et al, 2014, randomized patients to Xadago 50 mg/day (n=223), Xadago 100 mg/day (n=224), or placebo (n=222). Xadago 50 mg/day and 100 mg/day significantly increased "ON" Time compared to placebo ([0.51 hours (0.07, 0.94); p=0.0223]; [0.55 hours (0.12, 0.99); p=0.0130]). The increase in "ON" Time without troublesome dyskinesia was accompanied by a similar significant reduction in "OFF" Time (p=0.0043; p=0.0034) and a reduction in Unified Parkinson's Disease Rating Scale Part III (UPDRS III) scores assessed during "ON" Time (p=0.0006; p=0.0138). Withdrawal rates were 6.1%, 5.6%, and 6.9% for the placebo group, Xadago 50 mg/day group, and Xadago 100 mg/day group respectively and represent incomplete trials due to adverse reactions, lack of efficacy, non-compliance and withdrawal of consent.[2]

Schapira et al, 2016, randomized patients to Xadago 100 mg/day (N=274) or placebo (N=275). Xadago was significantly better than placebo for increasing "ON" Time ([0.96 hours (0.56, 1.37); p<0.001]). The increase in "ON" Time without troublesome dyskinesia was accompanied by a similar significant reduction in "OFF" Time (p<0.001) and a reduction in UPDRS III scores assessed during "ON" Time (p=0.003). Withdrawal rates were 12.4% and 10.6% for the placebo and treatment groups respectively and represent incomplete trials due to adverse reactions, lack of efficacy, non-compliance and withdrawal of consent.[3]

CONTRAINDICATIONS
Xadago is contraindicated in patients with:
- Concomitant use of the following drugs:
  - Other monoamine oxidase inhibitors or other drugs that are potent inhibitors of monoamine oxidase (e.g., linezolid)
  - Opioid drugs (e.g., tramadol, meperidine and related derivatives); selective norepinephrine reuptake inhibitors; tri- or tetra-cyclic or triazolopyridine antidepressants; cyclobenzaprine; methylphenidate, amphetamine, and their derivatives; St. John's wort
  - Dextromethorphan
- A history of a hypersensitivity to safinamide
- Severe hepatic impairment (Child-Pugh C: 10-15)

CENTENE PHARMACY AND THERAPEUTICS
NEW DRUG REVIEW
3Q17 July – August

BLACK BOX WARNINGS
Not applicable

DRUG INTERACTIONS
- MAO inhibitors: Hypertensive crisis
- Opioid drugs: Death
- Selective Serotonin Reuptake Inhibitors: Serotonin syndrome
- Dextromethorphan: Psychosis
- Sympathomimetics: Hypertensive crisis
- Tyramine: Hypertensive crisis
- Breast Cancer Resistance Protein (BCRP) substrates: Substrate toxicity
- Dopamine agonists: Worsening of PD symptoms

ADVERSE REACTIONS
Most common adverse reactions (incidence on XADAGO 100 mg/day at least 2% greater than placebo): Dyskinesia, fall, nausea, insomnia

DOSAGE AND ADMINISTRATION
- Initial dose: 50 mg administered orally once daily at the same time of day. After two weeks the dose may be increased to 100 mg once daily based on individual need and tolerability.
- Hepatic impairment: Do not exceed 50 mg once daily in patients with moderate hepatic impairment. Xadago is contraindicated in patients with severe hepatic impairment.

PRODUCT AVAILABILITY
Tablets: 50 mg and 100 mg

THERAPEUTIC ALTERNATIVES[4-9]

DRUG NAME	USAGE REGIMEN (route of administration/frequency of use)	COMMENTS
Entacapone (Comtan)	Oral: 200 mg with each dose of levodopa/carbidopa up to a maximum of 8 times daily (maximum daily dose: 1600 mg).	COMP inhibitor AAN A rating (2006) Labeled for off time
Carbadopa/levodopa/ entacapone (Stalevo)	Oral: Dose should be individualized based on therapeutic response; doses may be adjusted by changing strength or adjusting interval. Fractionated doses are not recommended and only 1 tablet should be given at each dosing interval; maximum daily dose: 8 tablets of Stalevo 50, 75, 100, 125, or 150, or 6 tablets of Stalevo 200.	COMP inhibitor AAN A rating (2006) Labeled for PD - pivotal trials included off time.
Rasagiline (Azilect)	Oral: Monotherapy or adjunctive therapy (not	MAO B inhibitor

CENTENE PHARMACY AND THERAPEUTICS
NEW DRUG REVIEW
3Q17 July – August

DRUG NAME	USAGE REGIMEN (route of administration/frequency of use)	COMMENTS
	including levodopa): 1 mg once daily (maximum: 1 mg daily). Adjunctive therapy with levodopa: Initial: 0.5 mg once daily; may increase to 1 mg once daily based on response and tolerability (maximum: 1 mg daily).	AAN A rating (2006) Labeled for PD - pivotal trials included off time.
Ropinirole (Requip)	Oral: Recommended starting dose: 0.25 mg 3 times/day. Based on individual patient response, the dose should be titrated with weekly increments: Week 1: 0.25 mg 3 times/day; total daily dose: 0.75 mg; week 2: 0.5 mg 3 times/day; total daily dose: 1.5 mg; week 3: 0.75 mg 3 times/day; total daily dose: 2.25 mg; week 4: 1 mg 3 times/day; total daily dose: 3 mg. After week 4, if necessary, daily dosage may be increased by 1.5 mg/day on a weekly basis up to a dose of 9 mg/day, and then by 3 mg/day weekly to a total of 24 mg/day.	Dopamine agonist AAN B rating (2006) Labeled for PD - pivotal trials included off time.
Ropinirole (Requip XL)	Oral: Initial dose: 2 mg once daily for 1 to 2 weeks, followed by increases of 2 mg/day at weekly or longer intervals based on therapeutic response and tolerability; maximum: 24 mg/day.	Dopamine agonist AAN B rating (2006) Labeled for PD - pivotal trials included off time.
Pramipexole (Mirapex)	Oral: Initial dose: 0.125 mg 3 times daily, increase gradually every 5 to 7 days; maintenance (usual): 0.5 to 1.5 mg 3 times daily.	Dopamine agonist AAN B rating (2006) Labeled for PD - pivotal trials included off time.
Pramipexole (Mirapex ER)	Oral: Initial dose: 0.375 mg once daily; increase gradually not more frequently than every 5 to 7 days to 0.75 mg once daily and then, if necessary, by 0.75 mg per dose; maximum: 4.5 mg once daily.	Dopamine agonist AAN B rating (2006) Labeled for PD - pivotal trials included off time.
Rotigotine (Neupro)	Transdermal: Initial dose: 2 mg/24 hours for early-stage disease or 4 mg/24 hours for advanced-stage disease.	Dopamine agonist 6 mg/24 hours for early-stage disease; 8 mg/24 hours for advanced-stage disease.

Boldface indicates generic availability

CENTENE PHARMACY AND THERAPEUTICS
NEW DRUG REVIEW
3Q17 July – August

*Drugs in the table are limited to those with American Academy of Neurology (AAN) 2006 Level A and B ratings for treating wearing off time as well as the unrated drug rotigotine (Neupro; dopamine agonist) based on expert opinion. Drugs with AAN Level C ratings include apomorphine (Apokyn; dopamine agonist) and selegiline (Eldepryl; MAO B inhibitor). See National Parkinson Foundation Parkinson's Outcomes Project (Quality Improvement Initiative [QII]) available at www.Parkinson.org for current and pending PD findings – this 2009 multicenter global study has enrolled 9,000 patients to date and has published 8 preliminary papers not yet including medication management; its goal is to provide a standardized management protocol for Parkinson's disease.[10]

Utilization Management Recommendation

1) There is significant potential for inappropriate use and utilization management should be considered for the following reasons:
   a) To ensure appropriate use of medications that have a significant potential for use that may lead to inferior or unpredictable outcomes:
      i) Xadago is indicated for wearing off time when the desired therapeutic outcome in this regard has not been achievable with carbidopa/levodopa therapy;
      ii) Xadago is indicated as an adjunct to carbidopa/levodopa therapy.
2) Recommended utilization management tool(s): (check all that apply)
   (1) ☒ Prior authorization
   (2) ☐ Quantity limits
   (3) ☐ Provider newsletter
   (4) ☐ Hard block (plan exclusion)
   (5) ☐ Messaging
   (6) ☐ Electronic step therapy
   (7) ☐ Clinical Program

Product Comparison

- Equal therapeutic outcomes are anticipated for Xadago and the following drugs as adjuncts to carbidopa/levodopa therapy for wearing off time:
  - Entacapone (Comtan; generic)
    - CPAC score of 56 for Xadago versus Comtan
    - American Academy of Neurology (AAN) Level A rating for wearing off time
  - Rasagiline (Azilect, generic)
    - CPAC score of 56 for Xadago versus Azilect

- AAN Level A rating for wearing off time
- Ropinirole (Requip, Requip XL, generic)
  - AAN Level B rating for wearing off time
- Pramipexole (Mirapex, Mirapex ER, generic)
  - AAN Level B rating for wearing off time
- Rotigotine (Neupro)*
  - Non-inferiority study: Rotigotine vs pramipexole[9]

**FDA approval post AAN guideline publication.*

- It would be clinically appropriate to provide equal access to Xadago and any of the aforementioned drugs or to require a trial of one or more of the drugs before Xadago.
- It would not be appropriate to require either of the following drugs prior to Xadago:
  - Apomorphine (Apokyn; dopamine agonist)
    - AAN Level C rating for wearing off time
  - Selegiline (Eldepryl; MAO B inhibitor)
    - AAN Level C rating for wearing off time

REFERENCES

1. Xadago Prescribing Information. Louisville, KY: US WorldMeds, LLC; March 2017. Available at: http://xadago.com/. Accessed April 7, 2017.
2. Borgohain R, Szasz J, Stanzione P, et al. Randomized trial of safinamide add-on to levodopa in Parkinson's disease with motor fluctuations. Movement Disorders. 2014; 29(2): 229-237.
3. Schapira AHV, Fox SH, Hauser RA, et al. Assessment of safety and efficacy of safinamide as a levodopa adjunct in patients with Parkinson disease and motor fluctuations: A randomized clinical trial. JAMA Neurol. December 12, 2016. doi:10.1001/jamaneurol.2016.4467.
4. Pahwa MD, Factor SA, Lyons KE, et al. Practice Parameter: Treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review): Report of the Quality

Standards Subcommittee of the American Academy of Neurology. Neurology. April 2006; 66: 983-995.

5. Rinne UK, Larsen JP, Siden A, et al. Nomecomt Study Group. Entacapone enhances the response to levodopa in parkinsonian patients with motor fluctuations. Neurology. November 1998; 51(5): 1309-14.
6. Parkinson Study Group. Entacapone improves motor fluctuations in levodopa-treated parkinson's disease patients. Ann Neurol. 1997; 42: 747-755.
7. Rascol O, Brooks DJ, Melamed E, et al. Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily, study): a randomised, double-blind, parallel-group trial. Lancet. 2005; 365: 947-54.
8. Parkinson Study Group. A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations: The PRESTO study. Arch Neurol. 2205; 62: 241-248.
9. Poewe WH, Rascol O, Quinn N, et al. Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: A double-blind, double-dummy, randomized controlled trial. Lancet Neurol. June 2007; 6(6): 513-20.
10. Parkinson's Outcomes Project (Quality Improvement Initiative [QII]). The National Parkinson Foundation. Available at www.Parkinson.org. Accessed April 12, 2017.