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Subject: Dopamine Transporter Imaging with Single-Photon Emission Computed Tomography

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DESCRIPTION:

Dopamine transporter imaging with single-photon emission computed tomography (DaT-SPECT), using radiopharmaceutical ioflupane (^{123}I) injection, is a neuro-imaging modality being evaluated to improve the differential diagnosis of parkinsonian syndromes.

Dopamine transporter imaging with single-photon emission computed tomography (DaT-SPECT) is based on the selective affinity of dopamine transporter ligands for dopamine synthesizing neurons, which allows visualization of deficits in the nigrostriatal dopaminergic pathway.

Dopamine transporter ligands include iodine 123 2β-carbomethoxy-3β-(4-iodophenyl) tropane (123I-β-CIT), which is a cocaine analogue with affinity for both dopamine transporter and serotonin transporters. Intravenous 123I-β-CIT requires a delay between injection and scan of about 24 hours. Iodine 123 N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)nortropane (123I-FP-CIT) is a fluoropropyl derivate of β-CIT that is selective for brain striatal dopamine transporter, but can also bind to the serotonin transporter. Intravenous 123I-FP-CIT can be injected 3 to 6 hours before the scan (DaTscan). Other ligands with affinity for dopamine transporter include technetium 99m (2β((N,N-bis(2-mercaptoethyl) ethylene diamino)methyl) and 3β-(4-chlorophenyl) tropane (99mTc-TRODAT-1).

Binding of ligands with affinity and specificity for dopamine transporter ligands in the striatum is, in general, reduced in Parkinson disease (PD), genetic parkinsonism, dementia with Lewy bodies (DLB), corticobasal degeneration, progressive supranuclear palsy, and multiple system atrophy. In contrast, striatal DaT ligand binding is expected to be within the normal range in Alzheimer disease, essential tremor, dystonic tremor, orthostatic tremor, drug-induced parkinsonism, psychogenic parkinsonism, and vascular parkinsonism.

Visualization of striatal dopamine transporter binding, through DaT-SPECT, permits assessment of presynaptic dopaminergic deficit. It is proposed that an abnormal DaT-SPECT scan supports the diagnosis of PD, DLB, or other neurodegenerative parkinsonian syndrome, while a normal DaT-SPECT scan in a symptomatic patient supports the diagnosis of a disease not affecting the nigrostriatal dopaminergic pathway. There are, however, a significant percentage of patients with clinically diagnosed PD who do not show reduced DaT-SPECT binding. Patients with clinically diagnosed PD, who present with a normal DaT-SPECT scan, are referred to in the literature as "scans without evidence of dopaminergic deficit" (SWEDD). While many of these patients are ultimately diagnosed with non-PD syndromes, a portion of patients with normal DaT-SPECT imaging are confirmed to have PD by the reference standard. Additional research may shed light on these cases.

Analysis of DaT-SPECT images can be visual, semiquantitative, or quantitative. Because patients typically do not become symptomatic before a substantial number of striatal synapses have degenerated, visual interpretation of the scan is thought to be sufficient for clinical evaluation. A variety of methods are being tested to improve the validity and reliability of ratings, including commercially available software to define the region of interest for analysis and the development of an atlas for visual interpretation.

In 2011, the FDA approved [^{123}I]ioflupane ([^{123}I]-fluoropropyl βCIT), a dopamine transporter (DAT) radioligand, for SPECT. DaTscan (Ioflupane I 123 Injection) is a radiopharmaceutical indicated for striatal dopamine transporter visualization using single photon emission computed tomography (SPECT) brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian syndromes (PS). In these patients, DaTscan may be used to help differentiate essential tremor from tremor due to PS (idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy). DaTscan is an adjunct to other diagnostic evaluations.

Summary and Analysis of Evidence: The authors (Grosset et al 2014) presented a comprehensive analysis of the safety of dopamine transporter (DaTscan) starting from initiation of clinical development through 13 y after the date of first market approval. Safety data in the sponsor's clinical development safety database from 10 completed DaTscan clinical trials were pooled, and postapproval experience was summarized from standardized aggregate safety reports submitted to regulatory agencies. A total of 1,180 clinical trial subjects (92% of 1,284 subjects planned to receive DaTscan in the clinical trials) received DaTscan. Percentages of subjects with adverse events by category were as follows: all (22%), considered at least possibly related to DaTscan by the investigator (4%), any severe (3%), headache (4%), nausea (2%), dizziness (2%), nasopharyngitis (1%), and injection site hematoma (1%). Four percent of subjects had at least 1 serious adverse event; 5 subjects (<1%) had serious adverse events that led to death. All serious adverse events, including those that led to death, were deemed by an expert clinician to be unrelated to DaTscan. An estimated half a million market doses of DaTscan (for single use) were administered from July 2000 through the July 2013 reporting period. In postapproval safety assessment, 1 death was reported 20 d after (and unrelated to) DaTscan administration. Two spontaneously reported serious adverse drug reactions (ADRs) and 32 spontaneously reported nonserious ADRs were submitted, approximately half of which are identified in labeling. Headache (in clinical trials) and injection site pain (postapproval) were the most commonly reported events or reactions. Although adverse events were reported for 1 in 5 clinical trial subjects, most were mild and considered unrelated to DaTscan administration. Severe events were uncommon, and no serious adverse event occurring in more than 1 subject was deemed related to DaTscan administration. In postapproval experience, the

frequency of ADRs spontaneously reported was less than 1 per 10,000 doses administered. Comprehensive safety data show that DaTscan was well tolerated.

Bajaj et al, 2014 investigated the association between subject's Hoehn & Yahr (H&Y) stage, Mini-Mental State Examination (MMSE), age, and motor symptom subgroups and diagnostic performance of ioflupane [(123)I] imaging. Phase 4 study data were used to calculate sensitivity, specificity, positive and negative predictive value, and accuracy in 92 CUPS subjects, using 1-year clinical diagnosis after ioflupane [(123)I] imaging as reference standard. Diagnostic effectiveness of ioflupane [(123)I] imaging was high in all subgroups: 91% to 100% for H&Y low (<2) and high (≥2) stage subjects; 93% to 96% for MMSE low (<29) or high (≥29) scores; 91% to100% in both age subgroups (younger [<68] and older [≥68]); and 92% to 100% in subjects with both tremor dominant and balanced motor signs. Specificity of ioflupane [(123)I] imaging for bradykinetic rigid or posturally (BRP) unstable motor subtype was lower, but better than for baseline clinical diagnosis. The authors concluded that strongest diagnostic performance of ioflupane [(123)I] imaging for clinical diagnosis of Parkinson's syndrome (PS) or non-PS was associated with tremor and balanced motor dominance rather than with BRP dominance. High diagnostic effectiveness of ioflupane [(123)I] imaging and favourable performance relative to final clinical diagnosis at 1 year post-scan in subjects with CUPS was demonstrated. This study suggests that the diagnostic performance of ioflupane [(123)I] imaging in CUPS remains high at all stages of disease, including early stage, and across both age groups and cognitive state (MMSE).

POSITION STATEMENT:

Dopamine transporter imaging with single-photon emission computed tomography (DaT-SPECT) **meets the definition of medical necessity** when used for members with the following:

- Clinically uncertain Parkinson disease; **OR**
- Clinically uncertain dementia with Lewy bodies.

Dopamine transporter imaging with single-photon emission computed tomography (DaT-SPECT) for all other indications, including but not limited to monitoring of disease progression is considered **experimental or investigational**. The evidence is insufficient to determine the effects of dopamine transporter imaging with single-photon emission computed tomography (DaT-SPECT) on health outcomes.

BILLING/CODING INFORMATION:

CPT Coding:

There is no specific CPT code for dopamine transporter imaging.

HCPCS Coding:

A9584	Iodine I-123 ioflupane, diagnostic, per study dose, up to 5 millicuries

ICD-10 Diagnosis Codes That Support Medical Necessity:

G20	Parkinson's disease
G21.0-G21.9	Secondary parkinsonism

G31.83	Dementia with Lewy bodies

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) was found at the time of the last guideline reviewed date.

DEFINITIONS:

Parkinsonian syndromes: a group of movement disorders characterized by tremor, bradykinesia, and rigidity.

RELATED GUIDELINES:

FDG-SPECT, 04-78000-15

OTHER:

Other names used to report Dopamine transporter imaging with single-photon emission computed tomography (DaT-SPECT):

Note: The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

DaT neuroimaging
DaTscan
DAT-SPECT
DaT SPECT scan
Dopaminergic neuroimaging
Dopamine transporter imaging
Dopamine transporter (DaT) scan
Dopamine transporter scan (DaTSCAN)

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Medical Policy and Coverage Committee on 12/05/24.

GUIDELINE UPDATEINFORMATION:

02/15/18	New Medical Coverage Guideline.
11/15/18	Review; no change to position statement, Updated references.
12/15/18	Revision; added position statement for clinically uncertain Parkinson disease and clinically uncertain dementia with Lewy bodies. Revised experimental investigational position statement. Added diagnoses codes (G20, G21.0-G21.9, G31.83). Updated references.
12/15/20	Review/revision; no change to position statement. Deleted code 78607. Updated references.
12/15/21	Review; no change to position statement. Updated references.

12/15/23	Review; no change to position statement. Updated references.
12/15/24	Review; no change to position statement. Updated references.