Paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) or paediatric acute neuropsychiatric disorders (PANS)

Condition for which Ig use is in exceptional circumstances only

Specific Conditions	• Paediatric autoimmune neuropsychiatric disorder (PANDAS) • Paediatric acute neuropsychiatric disorders (PANS)
Indication for Ig Use	• Paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) or paediatric acute neuropsychiatric disorders (PANS) unresponsive to trial of antibiotic therapy, and significant impairment requiring intervention • Relapse of paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) or paediatric acute neuropsychiatric disorders (PANS) symptoms within three months of commencement of trial off Ig therapy
Level of Evidence	Evidence of probable benefit – more research needed (Category 2a)
Description and Diagnostic Criteria	Paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) was first described in the early 1990s. PANDAS is characterised by rapid-onset tics associated with obsessive-compulsive disorder (OCD) in the context of recent streptococcal infection. Molecular mimicry between streptococcal antigens and the central nervous system is thought to underlie the cause. Symptomatic therapy is used with variable response. It has been observed that streptococcal infection is not the only trigger of acute neuropsychiatric disorders, but other infectious agents can also trigger acute neuropsychiatric events. For this reason, the term paediatric acute neuropsychiatric disorders (PANS) was added. PANDAS and PANS have remained controversial entities, partly due to the absence of a reliable and available biomarker. The diagnosis remains based upon the clinical syndrome. The hallmark of these diseases is the very rapid acute onset of emotional lability, OCD, tics and a 'change in behaviour' that occurs in the days or weeks after an infectious trigger. Swedo et al (1998) define the presentation: I. Abrupt, dramatic onset of obsessive-compulsive disorder or severely restricted food intake II. Concurrent presence of additional neuropsychiatric symptoms, (with similarly severe and acute onset), from at least two of the following seven categories: 1. Anxiety 2. Emotional lability and/or depression, irritability, aggression, and/or severely oppositional behaviors 3. Behavioural (developmental) regression 4. Deterioration in school performance (related to attention - deficit/hyperactivity disorder [ADHD]-like symptoms, memory deficits, cognitive changes) 5. Sensory or motor abnormalities 6. Somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency 7. Symptoms are not better explained by a known neurologic or medical disorder. Unlike Tourette syndrome and idiopathic OCD (which tend to wax and wane in severity), PANDAS and PANS have a 'shark tooth' pattern of disease severity with infection triggered severe episodes, followed by complete remissions. The episodes tend to reoccur, and the ability to achieve complete remissions tends to decline with time, resulting in potential persistent symptoms. PANDAS and PANS are probably rare conditions, and it is important to distinguish the entity from 'idiopathic' Tourette syndrome or OCD. The hallmark of the disease remains the infection triggered acute onset of neuropsychiatric change. A trial of antibiotics can be used first but if this is inadequate, and the patient is significantly impaired, a trial of steroid, or intravenous immunoglobulin (IVIg) can be considered. A consensus definition of PANS was proposed in 2015 although the definition has not been tested by independent observers (Chang et al, 2015). Given the rarity and controversy of the entities, it is recommended to seek second opinion from specialists with expertise in the field.
Justification for Evidence Category	A single randomised placebo-controlled trial using intravenous immunoglobulin (IVIg) for paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) showed prolonged and significant improvement in obsessive-compulsive symptoms, anxiety, depression, emotional lability and overall function compared with placebo. Improvements in symptoms were still evident at one-year follow-up. A futher uncontrolled retrospective description of 12 individuals with PANDAS described benefit when

using 2g/kg of IVIg in the first course or 1 to 1.5g/kg of IVIg for further doses.

The single randomised controlled trial supported the use of IVIg in PANDAS. However there has been no further study to confirm this finding.

Diagnosis Requirements

A diagnosis must be made by an Immunologist or a Neurologist.

Qualifying Criteria for Ig Therapy

Paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) or paediatric acute neuropsychiatric disorders (PANS) unresponsive to trial of antibiotic therapy, and significant impairment requiring intervention

This indication is for patients who have not trialled off Ig therapy for PANS/PANDAS in the previous three months. Any patients who have, and have since relapsed, should apply for Ig therapy under the indication: **Relapse of paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) or paediatric acute neuropsychiatric disorders (PANS) symptoms within three months of commencement of trial off Ig therapy**

- Abrupt, dramatic onset of obsessive-compulsive disorder or severely restricted food intake associated with infection

  AND

- Concurrent additional neuropsychiatric symptoms from at least two of the categories as described by Swedo et al, 1998 (see diagnostic criteria), and other known neurologic or medical disorders have been excluded

  AND

- Disability as measured by an adapted Modified Rankin Scale (MRS) score of three points or greater

  AND

- No clinical response has been achieved following standard antibiotic therapy

Review by a neurologist or immunologist is required within one month of treatment to determine whether the patient has responded.

For stable patients on maintenance treatment, review by a neurologist or immunologist is required at least three monthly. Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.

Relapse of paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) or paediatric acute neuropsychiatric disorders (PANS) symptoms within three months of commencement of trial off Ig therapy

This indication is for patients who have had a **Relapse of paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections** (**PANDAS) or paediatric acute neuropsychiatric disorders (PANS) symptoms within three months of commencement of trial off Ig therapy.** Any patients who have not trialled off Ig therapy for PANDAS/PANS in the last six months should apply for Ig therapy under the indication: **Paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections** (**PANDAS) or paediatric acute neuropsychiatric disorders (PANS) unresponsive to trial of antibiotic therapy, and significant impairment requiring intervention.**

- Trial off Ig therapy occurred within the last six months

  AND

- Patient had a positive response to previous Ig therapy including improvement in signs, symptoms and/or disability

  AND

- Relevant formal assessment methods indicate worsening of symptoms post Ig therapy (Tics-Yale or OCD-CY-BOCS or Anxiety –SPENCE)

  AND

- Current disability is demonstrated as measured by an adapted Modified Rankin Scale (MRS) score of least three points

Review by a neurologist is required within one month of treatment to determine whether the patient has responded, and three monthly thereafter.

For stable patients on maintenance treatment, review by a neurologist or immunologist is required at least three monthly. Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.

Review Criteria for Assessing the Effectiveness of Ig Use

Paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) or paediatric acute neuropsychiatric disorders (PANS) unresponsive to trial of antibiotic therapy, and significant impairment requiring intervention

Review by a neurologist or imumunologist is required within one month of treatment to determine whether the patient has responded.

For stable patients on maintenance treatment, review by a neurologist or immunologist is required at least three monthly. Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.

Clinical effectiveness of Ig therapy can be assessed by:

On review of the initial authorisation period

- Improvement or stabilisation in the severity of neuropsychiatric symptoms and function as compared to the qualifying assessment

  AND

- Relevant formal assessment methods are used to monitor the response to Ig therapy (Tics-Yale or OCD-CY-BOCS or Anxiety –SPENCE)

  AND

- Improvement or stabilisation in disability as measured by an adapted Modified Rankin Scale (MRS) score less than or equal to the score at the qualifying assessment

On review of a continuing authorisation period

- Improvement in neuropsychiatric symptoms and function compared to the previous assessment

  AND

- Relevant formal assessment methods are used to monitor the response to Ig therapy (Tics-Yale or OCD-CY-BOCS or Anxiety –SPENCE)

  AND

- Improvement in disability is demonstrated as measured by an adapted Modified Rankin Scale (MRS) score that is less that the score at qualifying, and less than or equal to the score at the previous review assessment

  AND

- A trial of weaning towards cessation of Ig therapy is planned for clinically stable patients or a valid reason why a trial is not planned or contraindicated at this time

Relapse of paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) or paediatric acute neuropsychiatric disorders (PANS) symptoms within three months of commencement of trial off Ig therapy

Review by a neurologist or immunologist is required within one month of treatment to determine whether the patient has responded.

For stable patients on maintenance treatment, review by a neurologist or immunologist is required at least three monthly. Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.

Clinical effectiveness of Ig therapy can be assessed by:

On review of the initial authorisation period

- Improvement or stabilisation in the severity of neuropsychiatric symptoms and function compared to the qualifying assessment

  AND

- Relevant formal assessment methods are used to monitor the response to Ig therapy (Tics-Yale or OCD-CY-BOCS or Anxiety –SPENCE)

  AND

- Improvement or stabilisation in disability as measured by an adapted Modified Rankin Scale (MRS) score less than or equal to the score at qualifying assessment

On review of a continuing authorisation period

- Improvement in neuropsychiatric symptoms and function compared to the previous assessment

  AND

- Relevant formal assessment methods are used to monitor the response to Ig therapy (Tics-Yale or OCD-CY-BOCS or Anxiety –SPENCE)

  AND

- Improvement in disability is demonstrated as measured by an adapted Modified Rankin Scale (MRS) score that is less than the score at qualifying and less than or equal to the score at the previous review assessment

  AND

- A trial of weaning towards cessation of Ig therapy is planned for clinically stable patients or a valid reason why a trial is not planned or contraindicated at this time

Dose

Paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) or paediatric acute neuropsychiatric disorders (PANS) unresponsive to trial of antibiotic therapy, and significant impairment requiring intervention

- **Induction Dose (IVIg)** - Up to 2g/kg in 2 to 5 divided doses.
- **Maintenance Dose (IVIg)** - 1-1.5 g/kg, 4 to 6 weekly.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Refer to the current product information sheet for further information on dose, administration and contraindications.

Relapse of paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) or paediatric acute neuropsychiatric disorders (PANS) symptoms within three months of commencement of trial off Ig therapy

- **Induction Dose (IVIg)** - Up to 2g/kg in 2 to 5 divided doses.
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The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

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