**2017 (v3.0) Proposed changes to v2.1 of the Criteria for the clinical use of intravenous immunoglobulin in Australia**

| **v2.1 CONDITION NAME: Paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS)**  **v3.0 CONDITION NAME: Paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) or Paediatric acute neuropsychiatric disorders (PANS)** | |
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| **PROPOSED APPROACH:**  **To retain PANDAS / PANS in *Exceptional circumstances only* with the changes as outlined.** | **SUMMARY OF RATIONALE:**  The recommended changes are supported by factors including that:   * This is a very rare condition with national Ig usage data in line with expected prevalence. * Streptococcal A consensus definition of PANS was proposed in 2015 and has been included in the qualifying criteria. * Streptococcal A infection is not the only trigger of acute neuropsychiatric disorders; other infectious agents can also trigger acute neuropsychiatric events. * Eligibility has been limited to patients that have failed to respond to corticosteroids or where corticosteroids are contraindicated. * Access has been strictly defined with initial review at one month to confirm response and three monthly monitoring thereafter with ongoing demonstration of continuing improvement in symptoms but with persistent disability to remain on Ig therapy. * This condition is listed in the Canadian IVIg Management Guidelines (Ontario Regional Blood Coordinating Network, 2016) and as a ‘grey’ condition in the UK NHS immunoglobulin guidelines (UK Department of Health, 2011). Indications are categorised as ‘grey’ if evidence is weak. The UK guidelines acknowledge that in many cases, this is because the disease is rare. Local approval is required to access IVIg for ‘grey’ indications. |
| **v2.1 CONDITION CATEGORY:** Condition for which Ig use is in Exceptional circumstances only(Chapter 7)  **v3.0 CONDITION CATEGORY:** Condition for which Ig use is in Exceptional circumstances only(Chapter 7) | |
| **Role of Ig therapy:** Patients should be treated with conventional therapies such as cognitive behavioural therapy and anti-obsessional medications e.g. Selective Serotonin Reuptake Inhibitors (SSRI), and where appropriate, antibiotics to treat the infection. Immune-based therapies are intended only for use in cases where the neuropsychiatric symptoms are related to an autoimmune response (hence the use of the specific diagnostic criteria) and in Australia, Ig will only be accessible once the patient has been proven to be unresponsive to corticosteroids or where corticosteroids are contraindicated.  Three monthly monitoring has been introduced with a requirement for appropriate formal assessment methods to be used to monitor the specific symptoms and be reported by prescribers along with clinical progress at each review. Patients must be continuing to improve but still have persistent symptoms to remain eligible for ongoing Ig therapy. There is not a protocol developed to manage chronic relapsing episodes and if patients relapse off treatment, they would need to formally re-qualify. It is recognised that treatment may need to extend over 12 months, but patients will eventually cease Ig therapy. | |

| **ITEM** | **CRITERIA v2.1** | **PROPOSED REVISIONS TO THE CRITERIA** | | | **SPECIALIST WORKING GROUP RATIONALE FOR ADDITIONS/CLARIFICATIONS** |
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| **Condition Name** | **Paediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS)** | **Paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) or Paediatric Acute Neuropsychiatric Disorders (PANS)** | | | Paediatric Acute Neuropsychiatric Disorders (PANS) has been included in the condition name as streptococcal infection is not the only trigger of acute neuropsychiatric disorders. |
| **Specialty** | Neurology | Neurology | | | No change |
| **Category** | *Exceptional circumstances only* | *Exceptional circumstances only* | | | No change |
| **Specific Conditions** | PANDAS/tic disorders | PANDAS;  PANS | | | Added PANS |
| **Level of Evidence** | Evidence of probable benefit – more research needed (Category 2a) | Evidence of probable benefit – more research needed (Category 2a) | | | No change |
| **Justification for Evidence Category** | 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 recovery from 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.  A single randomised placebo-controlled trial using intravenous immunoglobulin (IVIg) for PANDAS showed very 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 single randomised placebo-controlled trial using IVIg for 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 further uncontrolled retrospective description of 12 individuals with PANDAS described benefit when using 2g/kg of IVIg in the first course or 1-1.5g/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. | | | Redrafted after consultation of the literature. Some of the previous content is now covered within the “Description and Diagnostic Criteria” |
| **Indications** |  | **PANDAS or PANS unresponsive to trial of antibiotic therapy, and significant impairment requiring intervention.** | | | The indication has been more clearly described |
| **Description and Diagnostic Criteria** |  | 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 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 behaviours  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  III. 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 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. | | | A detailed description of the disorder has been drafted based on the best available evidence to assist in appropriate differential diagnosis of this condition from the more common disorders of Tourette’s syndrome and idiopathic obsessive-compulsive disorder. |
| **Diagnosis is required** |  | Yes | By which specialty | Neurologist Clinical Immunologist | Diagnosis must now be made by a Neurologist or a Clinical Immunologist as the underlying cause of the condition is an infection that mimics neural pathways. |
| **Diagnosis must be verified** | No | By which specialty |  |
| **Exclusion Criteria** |  |  | | | No change |
| **Qualifying Criteria** |  | * 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 following categories, and other known neurologic or medical disorders have been excluded:   - Anxiety  - Emotional lability and/or depression  Irritability, aggression, and/or severely oppositional  behaviours  - Behavioural (developmental) regression  - Deterioration in school performance (related to attention-  deficit/hyperactivity disorder [ADHD]-like symptoms,  memory deficits, cognitive changes)  - Sensory or motor abnormalities  - Somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency  AND   * Disability as measured by the Modified Rankin Score of three points or greater   AND   * No clinical response has been achieved following standard antibiotic therapy   AND   * No clinical response to oral steroid therapy.   OR   * Steroid therapy is contraindicated. | | | The new qualifying criteria were developed based on Swedo et al (1998) and Chang et al (2015), and were endorsed by Specialist Working Group consensus.  The abrupt nature of the onset is a key feature that will be confirmed together with symptoms complying with the diagnostic criteria.  The Modified Rankin Score has been adapted to this condition given that there is no loss of motor function. For example,  0 - No symptoms at all  1 - No significant disability despite symptoms; able to carry out all usual activities  2 - Slight disability; but able to carry out all usual activities  3 - Moderate disability; loss of function compared to peer related norms  4 - Moderately severe disability; significant loss of function requiring assistance and unable to function without assistance  5 - Severe disability; and requiring constant attention |
| **Review Criteria** |  | Review by a Neurologist is required within 1 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 3 monthly. Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.  **On review of the initial authorisation period**  Clinical effectiveness of Ig therapy can be demonstrated by:   * Improvement 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 in disability as measured by Modified Rankin Score as compared to the qualifying assessment   **On review of a continuing authorisation period**  Clinical effectiveness of Ig therapy can be demonstrated by:   * Improvement in neuropsychiatric symptoms and function compared to the previous review 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 Modified Rankin Score as compared to the previous review assessment | | | At initial review, improvement in the severity of symptoms must be demonstrated for Ig therapy to be re-authorised. Relevant formal assessment methods must have been used in the assessment - these are suggested, however the variability in symptoms is such that a single methodology cannot be stipulated. For example;   1. Tic as measured by Yale Scale 2. OCD as assessed by CY-BOCS 3. Anxiety as assessed by SPENCE   The Modified Rankin is maintained as the standard assessment method for disability.  The authorisation of continuing Ig therapy will be dependent on improvement being consistently demonstrated but symptoms and disability persisting. |
| **Dose** | Refer to the current product information sheet for further information.  The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient. | **Induction Dose**– Up to 2g/kg in 2 to 5 divided doses  Review after 1 month, if improvement demonstrated but symptoms persist, further courses can be considered every three months.  **Maintenance Dose** –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.** | | | Induction and maintenance doses have been developed and agreed by Specialist Working Group consensus. |

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| **References**  **(most recent update: February 2016)** |
| Chang K, Frankovich J, Cooperstock M, Cunningham M, Latimer M, Murphy T, et al (2015) Clinical Evaluation of youth with pediatric Acute-onset neuropsychiatric Syndrome (PANS): Recommendations from the 2013 PANS Consensus Conference. *Journal of Child and Adolescent Psychopharmacology*, 25:3-13.  <https://www.ncbi.nlm.nih.gov/pubmed/25325534>  Kovacevic M, Grant P and Swedo SE (2015) Use of Intravenous Immunoglobulin in the treatment of 12 Youths with pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections. *Journal of Child and Adolescent Psychopharmacology*, 25:65-69.  Swedo SE, Leonard HL, Garvey M, Mittleman B, Perlmutter S, Lougee L, et al (1998) Pediatric Autoimmune Neuropsychiatric Disorders associated with Streptococcal Infections: Clinical description of the first 50 cases. *American Journal of Psychiatry*, 155:264-271.  <https://www.ncbi.nlm.nih.gov/pubmed/9464208>  Singer HS (1999) PANDAS and immunomodulatory therapy. *Lancet*, 354(9185):1137–8.  <https://www.ncbi.nlm.nih.gov/pubmed/10513701>  Ontario Regional Blood Coordinating Network (2016). Ontario Intravenous Immune Globulin (IVIG) Utilization Management Guidelines, Version 3.0. [online]. Available at: http://transfusionontario.org/en/download/ontario-intravenous-immune-globulin-IVIg-utilization-management-guidelines-2/.  Perlmutter SJ, Leitman SF, Garvey MA, Hamburger S, Feldman E, et al (1999) Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. *Lancet,* 354(9185):1153–8.  <https://www.ncbi.nlm.nih.gov/pubmed/10513708>  UK Department of Health (2011) Clinical Guidelines for Immunoglobulin Use: Second Edition Update. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment\_data/file/216671/dh\_131107.pdf  UK Department of Health (2011) Clinical Guidelines for Immunoglobulin Use: Second Edition Update: Summary Poster. Available at: https://www.igd.nhs.uk/wp-content/uploads/2016/04/DemandManagementPoster\_v4\_February2016.pdf |

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| **POTENTIAL OPERATIONAL IMPACT** | | | | | | |
| The revised criteria provide significantly greater guidance for access to Ig therapy and patient management and a neurologist or clinical immunologist will be required to make the diagnosis and manage patient treatment. Patients will be required to be assessed at qualifying and review using a Modified Rankin Scale, however, the scale will be presented as ‘drop-down’ menu options within BloodSTAR v3.0 and will be simple to apply. Increased data entry will be required compared to the current Ig request process.  This condition is very rare and the operational impact is considered to be marginal, except that each ongoing treatment is only approved for the next three-month period, so the few patients on therapy, three monthly monitoring will be required to continue Ig therapy. It is anticipated that these patients would normally be seen at least this frequently by neurologists. Access to Ig therapy will only continue if the patient’s symptoms can be demonstrated to continue to improve but the patient has persistent disability. Eventually, Ig therapy will be ceased. | | | | | | |
| **POTENTIAL IMPACT ON PATIENTS, DEMAND AND EXPENDITURE** | | | | | | |
| **Description of impact on patients:** | | There is not anticipated to be any significant impact on patients as a result of these criteria given that they are based on how specialists already diagnose and manage patients with PANDAS/PANS. The formal access criteria proposed require that a neurologist or an immunologist makes the diagnosis and manages the patient treatment. This is because it is rare and it’s important to ensure its correct diagnosis and treatment. The underlying cause of the condition is an infection that causes episodes of disturbances in emotions, behaviour, thinking skills, movement and/or sleep.  For existing patients on Ig maintenance therapy, three monthly reviews are required to assess the effectiveness of the treatment to improve both symptoms and the remaining degree of disability. Given that patients will already require regular review by their specialist, this requirement will not place an added burden on patients. If Ig therapy has not been effective in continuing to demonstrate improvement each three months, it will be ceased as a different treatment should be used. If patients continue to improve, they will eventually no longer require Ig treatment. The decision to cease Ig therapy will be based on the patient’s response. If patients relapse, a further request for Ig therapy may be made.  New patients authorised to receive Ig therapy will require an initial check after the first month of Ig treatment to confirm that Ig therapy is effective. If improvement has been demonstrated, Ig therapy will be continued; otherwise a different treatment would be required. The ongoing arrangements for maintenance therapy are as outlined above for existing patients. | | | | |
| **Impact on demand** | | There has previously been no access criteria defined for this condition. The development of access criteria (requiring first line treatment with corticosteroids) and the new requirements for review and monitoring may reduce the number of patients being treated and the period of treatment with Ig therapy. The impact on overall demand levels however is expected to be very marginal, if any, as use is so low. | | | | |
|  | **2011-12** | **2012-13** | **2013-14** | **2014-15** | **2015-16** | The Specialist Working Group estimated magnitude of effect:  No impact against projected demand |
| **Patient number** | **6** | **6** | **<5** | **7** | **6** |
| **Total Grams issued** | **671** | **2,225** | **<2,000** | **2,161** | **1,447** |
| **% Total Grams issued** | **0.02%** | **0.06%** | **<0.04%** | **0.05%** | **0.03%** |
| **Specialist Working Group knowledge development opportunities and recommendations** | | | | | | |
| None identified at this stage. | | | | | | |

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| **END OF PUBLIC CONSULTATION DOCUMENT**  **Next review: Twelve to eighteen months from BloodSTAR v3.0 implementation** |