IMMUNO DEFICIENCY UK
Supporting families affected by primary and secondary immunodeficiency

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26th April 2023

Dear NICE,

Re: The decision by NICE of Leniolisib for activated phosphoinositide 3-kinase delta syndrome (APDS; ID6130) not meeting the HST criteria

We are writing as representatives of the patient group Immunodeficiency UK and BSI Clinical Immunology Professional Network to challenge the decisions made by NICE concerning HST routing of Leniolisib as a treatment for APDS.

Not meeting HST criterion 1:

We consider it wrong to use the prevalence of PIDs in general, as opposed to prevalence of APDS specifically, in making a judgement as to whether leniolisib meets criteria 1 of HST routing. This decision inherently implies that all primary immunodeficiency disorders (PIDs) are the same. This is not the case. By extensive research, and the use of genomics, over 485 different types of PID are now recognised and defined by phenotype and genotype[1]. This has helped clinicians better recognise the different fundamental causes of immune dysfunction and advance research into optimal treatments for specific PID conditions based on the understanding and characterisation of the underlying mechanisms at fault.

APDS is one specific type of PID and has been shown to be a result of a hyperactive PI3Kδ signalling pathway due to specific mutations in either PIK3CD or PIK3R which gives rise to immune deficiency, immune dysregulation and lymphoma. In the UK less than 50 people with this condition have been identified[2]. On this basis APDS meets the criteria of a rare disorder.

The failure of APDS to meet NICE's criterion 1 also throws into question the underlining principle of how NICE defines a rare disorder and has worrying implications for the assessment of targeted therapies for other PID conditions, and indeed for the wider rare disease community. The NICE decision is also at odds with the EMA decision and fundamentally undermines the foundations of the England's Rare Disease Action Plan 2023 and UK Rare Disease Plan. We find this of great concern.

We also note, for example, that this decision is not consistent with NICE's decision (April 2022) concerning HST approval of Elosulfase alfa for the treatment for Mucopolysaccharide (MPS) type 4A, despite MPS type 4A sharing all the common symptoms of the six other types of MPS which fall under the umbrella term of lysosomal disorders.

We ask that NICE urgently reconsiders its decision with respect to the condition APDS failing to meet HST criterion 1.

Not meeting HST criterion 3:

APDS is considered by the clinical community as a serious life-threatening condition. Lymphoma often presents by the late teens or in early adulthood and is one of the major complications of APDS. The cumulative risk of lymphoma and mortality is very high - estimated to be 78% at the age of 40 years[3].The drug Leniolisib reduces the inflammatory and autoimmune complications that may lead to lymphoma. Somatic mutations in Pi3K are seen in patients without APDS with lymphoma and the link between atypical cell survival/malignancy and this gene is very high and of all primary immunodeficiencies APDS carries the highest risk of lymphoma development.

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The variability in the symptoms affected by this disorder is not unexpected. It is widely known that the same genetic abnormality can cause different effects in different people. This variability results from the complicated interactions between genes and other factors related to the patient and his or her environment. The fact that gene defects can have such variable effects has been known for many years.

Not meeting HST criterion 4:

We dispute NICE's decision that Leniolisib does not offer significant additional benefit over other existing treatment options. There is no licensed therapy for this patient group that has been shown to be of benefit in a randomised control trial. There is a huge unmet need for a therapy that targets the cause of APDS rather than reliance on treatments that broadly manage the symptoms of immunodeficiency such as antibiotics, IG therapy etc. These therapies do not prevent the development of the herpes infections nor lymphoproliferative, autoimmune/inflammatory complications nor lymphoma in APDS. Leniolisib specifically targets the specific cause of APDS which will help improve patient care by reducing the lymphoproliferative and autoimmune complications without compromising protective immunity. Current approaches e.g., mTOR inhibitors may give rise themselves to increased malignancy risk and uncontrolled infection risk in the immunocompromised host.

We urge NICE to urgently reconsider their decision.

Yours sincerely,

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CEO
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Dr Sinisa Savic
Chair of the British Society for Immunology – Clinical Immunology Professional Network Steering Group

References:

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