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December 21, 2020

Re: Multisystem Inflammatory Syndrome in Children (MIS-C), Case definition & Reporting

As of December 8th 2020, just under 18% of COVID-19 positive cases were reported among school-aged children in Manitoba, with the highest proportion of cases (35%) reported among 15 to 19 year olds, followed by 6 to 11 years old (28.3%), 12 to 14 year olds (17.3%), 2 to 5 year olds (12.9%) and lastly, those under 2 years old (6.4%). For the most part, children and adolescents diagnosed with COVID-19 do well.

MIS-C, sometimes referred to as PIMS (paediatric inflammatory multisystem syndrome) is a rare acute inflammatory condition that has been temporally associated with COVID-19. Small clusters of cases have been predominantly reported in communities with high levels of COVID-19, often several weeks after the peak of cases. Pediatric patients presenting with MIS-C have at times, been described as having manifestations that are Kawasaki disease-like or toxic shock syndrome-like. They often require intensive care management and consultation with pediatric infectious diseases, rheumatology and cardiology.

The national MIS-C case definition is as follows (must meet all four criteria):

1. Is a child/ adolescent 0 - 19 years of age with fever lasting 3 days or longer
2. Has at least two of the following symptoms/manifestations:
   a. Rash **OR** bilateral non-purulent conjunctivitis **OR** muco-cutaneous inflammation signs (oral, hands or feet).
   b. Hypotension **OR** shock.
   c. Features of myocardial dysfunction **OR** pericarditis **OR** valvulitis **OR** coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP).
   d. Evidence of coagulopathy (by PT, PTT, elevated d-Dimers).
   e. Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain).
3. Has elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin.
4. Has no other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, or no alternative plausible diagnosis.

Note: Cases that meet the above definition should be reported regardless of COVID-19 diagnostic or serology test findings.

While MIS-C is not a reportable illness at this time, Manitoba Health, Seniors and Active Living (MHSAL) is working with the Public Health Agency of Canada (PHAC) to conduct enhanced MIS-C surveillance. Please report any suspected or confirmed MIS-C cases using the attached *Multisystem Inflammatory Syndrome in Children (MIS-C) Clinical Case Form (*https://www.gov.mb.ca/health/publichealth/surveillance/forms.html*).* Ensure that all relevant criteria are documented to confirm that they meet the national case definition. Forms should be faxed to the MHSAL Surveillance Unit at 204-948-3044 (confidential fax).

Sincerely,

Dr. Brent Roussin, MD, JD, MPH, FRCPC
Manitoba Chief Provincial Public Health Officer
Manitoba Health, Seniors and Active Living

Santina Lee, MD FRCPC
Medical Officer of Health
Communicable Disease Control

Manitoba
Health, Seniors and Active Living

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C) CLINICAL CASE FORM

CASE FORM

FORM UPDATES: ☐ _____ (YYYY-MM-DD) ☐ _____ (YYYY-MM-DD)
CIRCLE AND INITIAL CHANGES ON FORM IN DARK PEN OR PENCIL SO UPDATED INFORMATION CAN BE DISTINGUISHED.

I. CASE IDENTIFICATION

full features: subject > client details > client demographics > personal information

1. *LAST NAME	2. *FIRST NAME		3. *DATE OF BIRTH YYYY - MM - DD
4. *SEX ◯ FEMALE ◯ MALE ◯ INTERSEX ◯ UNKNOWN	5. *REGISTRATION NUMBER (FORMER MHSC) 6 DIGITS	6. *HEALTH NUMBER (PHIN) 9 DIGITS	7. ALTERNATE ID SPECIFY TYPE
8. *ADDRESS AT TIME OF DIAGNOSIS → ☐ ADDRESS IN FIRST NATION COMMUNITY			9. *CITY/TOWN/VILLAGE
10. *PROVINCE/TERRITORY	11. *POSTAL CODE A#A #A#		12. *PHONE NUMBER ###-###-####

II. INFECTION INFORMATION

full features: investigation > investigation details > disease summary

13. DISEASE: ☐ MIS-C

14. * CASE CLASSIFICATION ◯ CLINICAL ◯ NOT A CASE

15. * ☐ MEETS ALL 4 CLINICAL CRITERIA GROUPS BELOW (CHECK EACH APPLICABLE SIGN AND SYMPTOM)

*GROUP 1
☐ CHILD OR ADOLESCENT (AGED 0-19 YEARS) WITH FEVER LASTING 3 DAYS OR LONGER

*GROUP 2 – AT LEAST 2 OR MORE OF A, B, C, D, OR E:

A. ☐ RASH ☐ BILATERAL NON-PURULENT CONJUNCTIVITIS ☐ MUCO-CUTANEOUS INFLAMMATION SIGNS (ORAL, HANDS, OR FEET)

B. ☐ HYPOTENSION ☐ SHOCK

C. ☐ FEATURES OF MYOCARDIAL DYSFUNCTION ☐ PERICARDITIS ☐ VALVULITIS ☐ CORONARY ABNORMALITIES BY ECHO
☐ CORONARY ABNORMALITIES BY ELEVATED TROPONIN OR NT-PROBNP

D. ☐ EVIDENCE OF COAGULOPATHY (BY PT, PTT, OR ELEVATED D-DIMERS)

E. ☐ ACUTE GASTROINTESTINAL PROBLEMS (DIARRHEA, VOMITING, OR ABDOMINAL PAIN)

*GROUP 3 –
☐ HAS ELEVATED MARKERS OF INFLAMMATIN SUCH AS ESR, C-REACTIVE PROTEIN, OR PROCALCITONIN

*GROUP 4 –
☐ HAS NO OTHER OBVIOUS MICROBIAL CAUSE OF INFLAMMATION, INCLUDING BACTERIAL SEPSIS, STAPHYLOCOCCAL OR STREPTOCOCCAL SHOCK SYNDROMES, OR NO ALTERNATIVE PLAUSIBLE DIAGNOSIS

III. LABORATORY INFORMATION

full features: subject summary > lab summary

16. *COVID-19 POSITIVE LABORATORY TEST	◯ NO ◯ YES
17. TYPE OF TEST	◯ PCR/NAAT ◯ ANTIGEN ◯ SEROLOGY ◯ OTHER, PLEASE SPECIFY_____

IV. SIGNS AND SYMPTOMS

full features: investigation > signs & symptoms

*SYMPTOM ONSET DATE	YYYY-MM-DD

*** IDENTIFIES CRITICAL DATA ELEMENT OR SECTION TO BE COMPLETED. IF THIS DATA IS MISSING, THE FORM WILL BE RETURNED.**

Manitoba
Health, Seniors and Active Living

V. RISK FACTOR INFORMATION

full features: subject > risk factors

	YES	NO	UNKNOWN	DECLINED TO ANSWER	NOT ASKED
18. * CONTACT OF A NEW OR PREVIOUSLY DIAGNOSED COVID-19 CASE (CONFIRMED OR PROBABLE) IN THE LAST 2 MONTHS IF YES, PLEASE INCLUDE NAME, DOB AND PHIN OF CASE NAME: DOB: PHIN:	○	○	○	○	○
19. OTHER RISK FACTOR	○	○	○	○	○
20. *UNDERLYING ILLNESS (SPECIFY) SPECIFY	○	○	○	○	○

VII. *OUTCOMES

investigation > outcomes

☐ HOSPITALIZATION SPECIFY FACILITY	ADMISSION DATE YYYY-MM-DD DISCHARGE DATE YYYY-MM-DD	☐ ICU SPECIFY FACILITY	ADMISSION DATE YYYY-MM-DD DISCHARGE DATE YYYY-MM-DD

☐ FATAL SPECIFY DATE OF DEATH YYYY-MM-DD	☐ PENDING	☐ RECOVERED	☐ UNKNOWN	☐ OTHER SIGNIFICANT OUTCOME/SEQUELAE SPECIFY

OTHER OUTCOMES:
○ DETERIORATING ○ CONVALESCING ○ STABLE

VIII. *REPORTER INFORMATION

investigation > investigation details >
investigation > investigation details > close investigation

21. FORM COMPLETED BY (PRINT NAME) 23. SIGNATURE 24. FORM COMPLETION DATE: YYYY-MM-DD	22. FACILITY NAME / ADDRESS / PHONE NUMBER	REPORTER USE ONLY STAMP HERE

PLEASE SUBMIT THIS INVESTIGATION FORM BY SECURED FAX TO THE SURVEILLANCE UNIT AT MANITOBA HEALTH.
AFTER HOURS EMERGENCY PHONE FOR PUBLIC HEALTH ISSUES: (204) 788-8666.

THIS FORM IS ALSO AVAILABLE FOR DOWNLOAD IN A FILLABLE PDF FORMAT AT
http://www.gov.mb.ca/health/publichealth/surveillance/forms.html

* IDENTIFIES CRITICAL DATA ELEMENT OR SECTION TO BE COMPLETED. IF THIS DATA IS MISSING, THE FORM WILL BE RETURNED.

IPSEN
Innovation for patient care

December 22, 2020

Drug Information and Poison Control Centers
Faculties of Medicine
Faculties of Pharmacy
National Medical Associations
Pharmacies

RE: INCRELEX® (mecasermin) – New product DIN: 02509733 (10 mg/ml solution for injection)

This is to inform you of the recent approval by the Therapeutic Products Directorate of Health Canada of INCRELEX (mecasermin). INCRELEX is indicated for the treatment of growth failure in children and adolescents from 2 to 18 years with confirmed severe primary insulin-like growth factor-1 deficiency (SPIGFD). SPIGFD is defined by:

- **height standard deviation score ≤ –**3.0 and;
- basal IGF-1 levels below the 2.5th percentile for age and gender and;
- GH sufficiency.
- Exclusion of secondary forms of IGF-1 deficiency, such as malnutrition, hypopituitarism, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids.

SPIGFD includes patients with **mutations in the GH receptor (GHR) gene/Laron's syndrome, post**-GHR signaling pathway, and IGF-1 gene defects; they are not GH deficient, and therefore, they cannot be expected to respond adequately to exogenous GH treatment.

Pediatrics (2-18 years): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of INCRELEX in pediatric patients has been established; therefore, Health Canada has authorized an indication for pediatric use. The safety and efficacy of INCRELEX in children below the age of 2 have not been established and therefore INCRELEX is not recommended in children below the age of 2.

Please consult the full product monograph for information on *Contraindications, Warnings and Precautions* and *Adverse Reactions*.

DOSAGE AND ADMINISTRATION

Treatment with mecasermin should be directed by physicians who are experienced in the diagnosis and management of patients with growth disorders. The dose should be tailored specifically for each patient and **should be adjusted based on tolerability and weight. If a child's weight changes, the dose should be** adjusted to maintain a consistent mg/kg dosage. Preprandial glucose monitoring is recommended at treatment initiation and until a well-tolerated dose is established. If frequent symptoms of hypoglycemia or severe hypoglycemia occur, preprandial glucose monitoring should continue.

The recommended starting dose of INCRELEX is 0.04 to 0.08 mg/kg (40 to 80 mcg/kg) twice daily by subcutaneous injection. If INCRELEX is well-tolerated for at least one week, the dose may be increased by 0.04 mg/kg per dose to the maximum dose of 0.12 mg/kg given twice daily.

Doses greater than 0.12 mg/kg twice daily should not be exceeded as this may increase the risk of neoplasia and hypoglycemic effects.

If the recommended dose is not tolerated by the patient, treatment with a lower dose can be considered. Treatment success should be evaluated based on height velocities. The lowest dose that was associated with substantial growth increases on an individual basis was 0.04 mg/kg BID.

Special populations
Renal impairment
No studies have been conducted in children with SPIGFD with renal impairment.

Hepatic impairment
No studies have been conducted in children with SPIGFD with hepatic impairment.

Geriatrics (≥ 65 years)
The safety and effectiveness of INCRELEX in patients aged 65 and over has not been established.

OVERDOSAGE

Acute overdose could lead to hypoglycemia. Treatment of acute overdose should be directed at reversing hypoglycemia. Oral glucose or food should be consumed. If the overdose results in loss of consciousness, intravenous (IV) glucose or parenteral glucagon may be required to reverse the hypoglycemic effects.

Long-term overdose may result in signs and symptoms of acromegaly or gigantism. Overdosing may lead to supraphysiological IGF-1 levels and may increase the risk of benign and malignant neoplasm.

In case of an acute or a chronic overdose, INCRELEX must be discontinued immediately. If INCRELEX is restarted, the dose should not exceed the recommended daily dosage.

DOSAGE FORMS, PACKAGING, STORAGE and STABILITY

INCRELEX is supplied in a 5 ml multi-dose vial (type I glass) closed with a stopper (bromobutyl/isoprene polymer) and a seal (lacquered plastic). Each vial contains 4 ml of solution. Pack size of 1 vial.

Store in a refrigerator (2°C - 8°C). Do not freeze. The solution should be clear immediately after removal from the refrigerator. If the solution is cloudy, or contains particulate matter, it must not be injected.

Keep the vial in the outer carton in order to protect from light.

Chemical and physical in-use stability has been demonstrated for 30 days at 2°C to 8°C. From a microbiological point of view, once opened, the medicinal product may be stored for a maximum of 30 days at 2°C to 8°C.

If you have additional questions or would like to request a copy of the complete product monograph, please contact Ipsen Biopharmaceuticals Canada Inc. at 1-855-215-2288 or consult the Ipsen Biopharmaceuticals Canada Inc. website: https://www.ipsen.ca/therapeutic-areas/products/.

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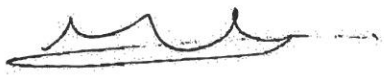
Best Regards,



Martine Hubert, M.D.
Head of Medical Affairs
Ipsen Biopharmaceuticals Canada Inc.

Reference:

1. Product Monograph: **INCRELEX™ (mecasermin).** Ipsen Biopharmaceuticals Canada Inc.; December 17, 2020.