Octreotide

Newborn use only

2022

Alert	Octreotide for hyperinsulinemic hypoglycaemia (HH) should only be prescribed in consultation with Paediatric Endocrinologist. **This formulary relates to short acting formulations of octreotide**. Long-acting formulations of octreotide (LAR - modified release injection) are beyond the scope of this formulary.
Indication	1. Congenital and acquired chylothorax 2. Hyperinsulinaemic hypoglycaemia
Action	Octreotide is somatostatin analogue. It inhibits growth hormone secretion, insulin secretion and glucagon secretion.[1] **Chylothorax:** The mechanism of action is uncertain. Octreotide is proposed to cause mild vasoconstriction of splanchnic vessels, including hepatic venous flow. This leads to reduction in gastric, pancreatic and intestinal secretions, inhibits gall bladder contraction and gastrointestinal motility, as well as intestinal absorption. These mechanisms collectively reduce the flow of chyle.[2, 3] **Hyperinsulinemic hypoglycaemia:** Octreotide inhibits the release of insulin secretion from pancreatic β-cells.[4, 5]
Drug type	Synthetic short-acting somatostatin analogue.
Trade name	Sandostatin solution for injection (Novartis), Octreotide GH, Octreotide Sun.
Presentation	Octreotide acetate solution for injection: 50 microgram/1 mL, 100 microgram/1 mL and 500 microgram/1 mL ampoules. **500 microgram/1 mL is the recommended strength for preparation of continuous IV infusion**. **50 microgram/1 mL or 100 microgram/1 mL are the recommended strengths for SC intermittent doses.**
Dose	<u>Chylothorax</u> **Continuous IV Infusion (recommended):** 1-10 microgram/kg/hour.*[2, 3, 6-10] Suggested regimen: Commence at 1-2 microgram/kg/hour, increase by 1-2 microgram/kg daily depending upon the response.* Doses up to 20 microgram/kg/hour have been used particularly in large volume chylothorax.[8,9] ***Large volume chylothorax:** Starting dose may be 4-5 microgram/kg/hour (ANMF consensus) and can be increased to a maximum of 20 microgram/kg/hour.[8, 9] **Subcutaneous (SC) injection:** 10-100 microgram/kg/**day** divided in 3-4 doses.[2, 3] <u>Hyperinsulinaemic hypoglycaemia</u> **SC intermittent injection (recommended):** Commence at 5 microgram/kg/**day** in 3-4 divided doses. Dose may be increased by 3-5 microgram/kg/**day** every 1-3 days to a maximum of 35 microgram/kg/**day** (ANMF consensus).[11-13] **SC continuous infusion:** Total daily SC dose can be given as a continuous 24-hour SC infusion, but requires an insulin pump. Discuss with Paediatric Endocrinologist.
Dose adjustment	Therapeutic hypothermia – No information. ECMO – No information. Renal impairment – No dose adjustment necessary.[14] Hepatic impairment – Half life may be increased in hepatic impairment.[14]
Maximum dose	Large volume chylothorax IV infusion: 20 microgram/kg/hour. Hyperinsulinaemic hypoglycaemia SC injection: 35 microgram/kg/**day**.
Total cumulative dose	
Route	IV, SC
Preparation	Allow solution to reach room temperature before use. **IV preparation** **Use 500 microgram/1 mL ampoule to prepare IV infusion:** Draw up 1 mL/kg (500 microgram/kg) of octreotide and add sodium chloride 0.9% to make a final volume of 50 mL with a final concentration of 10 microgram/kg/mL. **1 mL/hour = 10 microgram/kg/hour.** SC injection: Give undiluted.

	SC continuous infusion: To discuss with paediatric endocrine team on the preparation and dilution.
Administration	IV: Continuous infusion. SC: Injection or continuous infusion (discuss with Paediatric Endocrinologist). For intermittent SC injection: Rotate the site of injection.
Monitoring	Blood glucose levels, vital signs, liver function tests, full blood count
Contraindications	Hypersensitivity to octreotide or to any component of the formulation.
Precautions	Dose adjustments to medications e.g. diazoxide and insulin may be required during octreotide therapy due to its effect on glucose regulation.[14]
Drug interactions	Drug classes: Antipsychotics, antiarrhythmic agents, QT prolonging agents, somatostatin analogues. Concurrent use of the following drugs may result in increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest): Azithromycin, clarithromycin, chloral hydrate, ciprofloxacin, cotrimoxazole, erythromycin, fluconazole, foscarnet, phenothiazides, pentamadine, metronidazole, ondansetron, tacrolimus, sodium phosphate, voriconazole. Octreotide may decrease the metabolic clearance of drugs metabolised by CYP450 enzymes. Ciclosporin: Octreotide may reduce serum levels and effects of ciclosporin. Digoxin: Octreotide may decrease digoxin exposure.
Adverse reactions	Hyperglycaemia. Abdominal distension. Necrotising enterocolitis. Hypotension (can be severe). Pulmonary hypertension. Hepatitis and deranged liver functions. Cholelithiasis, cholecystitis with prolonged usage. Hypothyroidism or decreased thyroid stimulating hormone (TSH) with prolonged usage. Thrombocytopenia.
Compatibility	Fluids: Glucose 5%, sodium chloride 0.9%. **Sodium chloride 0.9% is the preferred infusion fluid for most indications as octreotide inhibits the release of insulin and affects blood glucose regulation.** Y-site: Aciclovir, alfentanil, allopurinol, amifostine, amikacin, aminophylline, amiodarone, amphotericin B conventional colloidal, amphotericin B lipid complex, amphotericin B liposome, ampicillin, anidulafungin, atenolol, atracurium, azithromycin, aztreonam, bivalirudin, buprenorphine, busulfan, calcium chloride, calcium gluconate, capreomycin, caspofungin, cefazolin, cefepime, cefotaxime, cefotetan, cefoxitin, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime, ciprofloxacin, clindamycin, dexamethasone, dexmedetomidine, digoxin, diltiazem, diphenhydramine, dobutamine, dopamine, doxycycline, enalaprilat, ephedrine, adrenaline (epinephrine), erythromycin lactobionate, esmolol, fentanyl, fluconazole, fluorouracil, foscarnet, fosphenytoin, furosemide, ganciclovir, gentamicin, glycopyrrolate, heparin, hydralazine, hydrocortisone, imipenem-cilastin, insulin regular, isoproterenol, labetalol, leucovorin, levofloxacin, lidocaine (lignocaine), linezolid, lorazepam, magnesium sulfate, meropenem, methadone, methotrexate, methylprednisolone, metronidazole, midazolam, milrinone, morphine, naloxone, nicardipine, nitroglycerin, nitroprusside sodium, norepinephrine, ondansetron, pamidronate, pancuronium, pentobarbital, phenobarbital (phenobarbitone), phentolamine, phenylephrine, piperacillin, piperacillin-tazobactam, potassium chloride, propranolol, ranitidine, remifentanil, rocuronium, sodium bicarbonate, sulfamethoxazole-trimethoprim, tacrolimus, ticarcillin, tobramycin, vancomycin, vasopressin, vecuronium, verapamil, voriconazole, zidovudine.
Incompatibility	Fluids: Lipid emulsion. Y-site: Cyclizine, micafungin, phenytoin.
Stability	Infusion solutions in sodium chloride 0.9% are stable for 24 hours below 25°C
Storage	Refrigerate between 2 to 8°C.* Do not freeze. Protect from light. *Sandostatin and GH brand of octreotide is stable at room temperature for up to 2 weeks. Ampoules unused after this period out of the fridge should be discarded.
Excipients	Sandostatin: Lactic acid, mannitol, sodium bicarbonate, water for injections.[14] Octreotide GH: Glycine, mannitol, dilute hydrochloric acid, water for injections. Octreotide Sun: Glacial acetic acid, sodium acetate trihydrate, sodium chloride and water for injections.

Special comments	
Evidence	**Efficacy** **Chylothorax:** Cochrane review by Das et al did not identify any randomised or quasi-randomised controlled trials and all the identified studies were case reports.[2] Of the 19 case reports of 20 neonates, 14 reported successful resolution of chylothorax. It was given either subcutaneously (SC) or intravenously (IV). The dose ranged between 10 to 70 microgram/kg/day SC and between 0.3 and 10 microgram/kg/hour as an IV infusion. The frequency of administration ranged from 6 to 24 hourly for SC and was mostly by continuous infusion for IV administration. The duration of administration varied between 4 and 21 days. Gastrointestinal intolerance, necrotising enterocolitis like illness and transient hypothyroidism were reported as side effects.[2] A systematic review by Bellini et al included 39 case reports. Octreotide was effective in 53% of congenital and 33% of acquired chylothorax.[7] The median initial dose was 2 microgram/kg/hour and the median maximum dose was 7.5 microgram/kg/hour, ranging from 1 to 20 microgram/kg/hour. Side effects were reported in 14.3% of patients. A prospective observational study from New South Wales evaluated the standard octreotide protocol in 6 neonates with congenital chylothorax. Octreotide was commenced at a median age of 13.5 days (range 8–22), given for a median duration of 20 days (range 12–27). The starting dose was 0.5–1 microgram/kg/hour with an increment of 1–2 microgram/kg/day to a maximum of 10 microgram/kg/hour. Resolution of chylothorax was achieved in 5 patients, being resistant to treatment in the 6th patient. None had adverse effects.[10] A 2018 Australian case series reported 11 neonates.[3] Ten out of 11 were preterm with gestation and birthweight ranging from 28 to 38 weeks and 908–3204 g respectively. The median duration of treatment was 17.5 days (7–26 days). Octreotide was administered as a continuous IV infusion in 9 cases. Octreotide was started at 1 microgram/kg/hour, increased by 1 microgram/kg daily to a maximum dose of 10 microgram/kg/hour. The maximum dose required for successful resolution was 4–10 microgram/kg/hour with a median of 8 microgram/kg/hour. SC octreotide (11–117 microgram/kg/day in three divided doses) was administered in 2 cases.[3] A 2017 case series by Yin et al reported 14 neonates with congenital chylothorax treated with either somatostatin or octreotide (1-6 microgram/kg/hour). Somatostatin/octreotide treatment reduced pleural drainage and respiratory support without significant side effects.[6] **High dose octreotide for chylothorax:** Doses to a maximum of 20 microgram/kg/hour have been suggested for large volume chylothorax and no significant side effects were reported at these higher doses in case reports.[8, 9] **Hyperinsulinaemic hypoglycaemia (HH):** Yorifuji et al treated 15 Japanese patients with diazoxide-unresponsive hyperinsulinism. They were treated with continuous SC infusion at a dosage of up to 25 microgram/kg/day. Octreotide was effective in all patients.[15] Hosokawa et al tested octreotide for HH through a combination of a single-arm, open-label clinical trial (SCORCH study) and an observational study (SCORCH registry). In the SCORCH study, 5 patients were treated with continuous **SC infusion** at a dose of 5-25 microgram/kg/day. In 3 patients, a clinically meaningful rise in blood glucose was achieved and therapy was continued. The SCORCH registry included 19 patients treated by SC octreotide, by continuous infusion or multiple daily injections. No serious adverse effects were observed in either of the studies.[5] Demirbilek et al reported on the usage of octreotide in 28 congenital hyperinsulinism infants. Octreotide was commenced at 5 microgram/kg/day as a continuous SC infusion with an incremental increase of 5 microgram/kg/day every 3–5 days to the maximum dose of 30 microgram/kg/day. Before discharge from the hospital, the SC infusion was changed to an equivalent dose in SC injections at 6-hour intervals.[11] Pan et al reported usage of octreotide in 7 small for gestational age neonates with HH who received octreotide at an initial dose of 5 microgram/kg/day through SC injections at **8-hour** intervals; dose was increased in increments of 2–5 microgram/kg/day every 3–5 days to the maximum dose of 30 microgram/kg/day.[16] All patients had a glycaemic response to octreotide, and no major adverse events were observed during the treatment.[16] McMahon et al reported octreotide use in 103 infants and children with HH. Octreotide was given SC in 53 of them and IV in 45 of them. Median (range) octreotide daily dose among 103 patients was 8.96 microgram/kg/day (1.33- 96 microgram/kg/day).[17] Laje et al reported octreotide usage in 192 infants with HH. They suggested an initial dose of 1-2 microgram/kg/day, increasing the dose as needed up to 40

	microgram/kg/day. They suggested daily dose can be divided every 6 or 12 hour intervals and either IV or SC route can be used.[18] Efficacy, dosing and side effects are summarised by experts in the field in 2 articles.[12, 13] **The expert consensus** recommends a dose of 5 microgram/kg/day SC in 6-8 hour interval and increasing to a maximum of 30-35 microgram/kg/day.[12, 13] The dose in this formulary is the consensus recommendation of the paediatric endocrine expert group of ANMF. **Safety** Doses used for treatment of chylothorax are larger than the dose required for treatment of hyperinsulinism. A systematic review by Bellini et al reported side effects in 14.2% of neonates treated with IV octreotide for chylothorax.[7] Adverse events were observed in term and preterm infants regardless of chylothorax aetiology, with the most severe cases (NEC and severe hypotension) occurring in the postoperative chylothorax. In addition, no association with octreotide dose and duration was observed. In the congenital chylothorax group, the following adverse events were reported: hyperglycaemia (1.7%), mild distended abdomen (1.7%), transient mild cholestasis (1.7%), transient hypothyroidism (1.7%), bloody stools (1.7%) and pulmonary hypertension (7%). In postoperative chylothorax, one case of necrotising enterocolitis (NEC), one case of hyperglycaemia and elevation of liver enzymes and one case of severe hypotension were reported. No association with octreotide dose and duration was observed.[7] There were other recent case reports of NEC with IV octreotide.[19] Side effects have also been reported with octreotide for hyperinsulinism but most side effects are mild and transient but there are case reports of hepatitis and NEC associated with the use of octreotide for hyperinsulinism.[5, 11, 15, 17, 18, 20-26] **Pharmacokinetics** The elimination half-life of octreotide is approximately 1.5 hours after both intravenous and subcutaneous administration.[1] Subcutaneous octreotide usually peaks within 30 minutes, and has a plasma duration of action of up to 12 hours.[1]
Practice points	
References	1. Octreotide. Micromedex online. Accessed on 22 March 2022. 2. Das A, Shah PS. Octreotide for the treatment of chylothorax in neonates. Cochrane Database of Systematic Reviews. 2010(9). 3. Zaki SA, Krishnamurthy MB, Malhotra A. Octreotide use in neonates: a case series. Drugs in R&D. 2018;18(3):191-8. 4. Da Lozzo P, Risso FM, Schleef J, Sirchia F, Sagredini R, Bussani R, et al. New Tools for Congenital Hyperinsulinism. Clinical Pediatrics. 2021;60(8):336-40. 5. Hosokawa Y, Kawakita R, Yokoya S, Ogata T, Ozono K, Arisaka O, et al. Efficacy and safety of octreotide for the treatment of congenital hyperinsulinism: a prospective, open-label clinical trial and an observational study in Japan using a nationwide registry. Endocrine Journal. 2017;64(9):867-80. 6. Yin R, Zhang R, Wang J, Yuan L, Hu L, Jiang S, et al. Effects of somatostatin/octreotide treatment in neonates with congenital chylothorax. Medicine. 2017;96(29):e7594. 7. Bellini C, Cabano R, De Angelis LC, Bellini T, Calevo MG, Gandullia P, et al. Octreotide for congenital and acquired chylothorax in newborns: A systematic review. J Paediatr Child Health. 2018;54(8):840-7. 8. Alhasoon MA. The use of high dose octreotide in management of neonatal chylothorax: Review. J Neonatal Perinatal Med. 2021;14(4):457-61. 9. Vass G, Evans Fry R, Roehr CC. Should Newborns with Refractory Chylothorax Be Tried on Higher Dose of Octreotide? Neonatology. 2021;118(1):122-6. 10. Shah D, Sinn JK. Octreotide as therapeutic option for congenital idiopathic chylothorax: a case series. Acta Paediatrica. 2012;101(4):e151-e5. 11. Demirbilek H, Shah P, Arya VB, Hinchey L, Flanagan SE, Ellard S, et al. Long-term follow-up of children with congenital hyperinsulinism on octreotide therapy. J Clin Endocrinol Metab. 2014;99(10):3660-7.

12. Giri D, Hawton K, Senniappan S. Congenital hyperinsulinism: Recent updates on molecular mechanisms, diagnosis and management. Journal of Pediatric Endocrinology and Metabolism. 2021.
13. Demirbilek H, Hussain K. Congenital hyperinsulinism: diagnosis and treatment update. Journal of clinical research in pediatric endocrinology. 2017;9(Suppl 2):69.
14. Octreotide. MIMS online. Accessed on 22 March 2022.
15. Yorifuji T, Kawakita R, Hosokawa Y, Fujimaru R, Matsubara K, Aizu K, et al. Efficacy and safety of long-term, continuous subcutaneous octreotide infusion for patients with different subtypes of KATP-channel hyperinsulinism. Clinical endocrinology. 2013;78(6):891-7.
16. Pan S, Zhang M, Li Y. Experience of Octreotide Therapy for Hyperinsulinemic Hypoglycemia in Neonates Born Small for Gestational Age: A Case Series. Hormone research in paediatrics. 2015;84(6):383-7.
17. McMahon AW, Wharton GT, Thornton P, De Leon DD. Octreotide use and safety in infants with hyperinsulinism. Pharmacoepidemiol Drug Saf. 2017;26(1):26-31.
18. Laje P, Halaby L, Adzick NS, Stanley CA. Necrotizing enterocolitis in neonates receiving octreotide for the management of congenital hyperinsulinism. Pediatric diabetes. 2010;11(2):142-7.
19. Chandran S, Agarwal A, Llanora GV, Chua MC. Necrotising enterocolitis in a newborn infant treated with octreotide for chylous effusion: is octreotide safe? BMJ Case Rep. 2020;13(2):11.
20. Alsaedi AA, Bakkar AA, Kamal NM, Althobiti JM. Late presentation of necrotizing enterocolitis associated with rotavirus infection in a term infant with hyperinsulinism on octreotide therapy: A case report. Medicine. 2017;96(40):e7949.
21. Avatapalle B, Padidela R, Randell T, Banerjee I. Drug-induced hepatitis following use of octreotide for long-term treatment of congenital hyperinsulinism. BMJ Case Rep. 2012;30:30.
22. Ben-Ari J, Greenberg M, Nemet D, Edelstein E, Eliakim A. Octreotide-induced hepatitis in a child with persistent hyperinsulinemia hypoglycemia of infancy. J Pediatr Endocrinol Metab. 2013;26(1-2):179-82.
23. Hawkes CP, Adzick NS, Palladino AA, De Leon DD. Late Presentation of Fulminant Necrotizing Enterocolitis in a Child with Hyperinsulinism on Octreotide Therapy. Hormone research in paediatrics. 2016;86(2):131-6.
24. Koren I, Riskin A, Barthlen W, Gillis D. Hepatitis in an infant treated with octreotide for congenital hyperinsulinism. J Pediatr Endocrinol Metab. 2013;26(1-2):183-5.
25. Levy-Khademi F, Irina S, Avnon-Ziv C, Levmore-Tamir M, Leder O. Octreotide-associated cholestasis and hepatitis in an infant with congenital hyperinsulinism. J Pediatr Endocrinol Metab. 2015;28(3-4):449-51.
26. Ros-Perez P, Golmayo L, Cilleruelo ML, Gutierrez C, Celaya P, Lacamara N, et al. Octreotide-related exocrine pancreatic insufficiency (EPI) in congenital hyperinsulinism. J Pediatr Endocrinol Metab. 2020;33(7):947-50.

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