Dinutuximab beta and Isotretinoin Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Status
For the treatment of high-risk neuroblastoma in patients aged 12 months and above, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and stem cell transplantation, as well as patients with history of relapsed or refractory neuroblastoma, with or without residual disease. Prior to the treatment of relapsed neuroblastoma, any actively progressing disease should be stabilised by other suitable measures.	C74.9	P00548a	Hospital

**If the reimbursement status is not defined [!], the indication has yet to be assessed through the formal HSE reimbursement process.*

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patient's individual clinical circumstances.

Cycle 1

- Cycle 1 consists of 14 days of isotretinoin alone and is given after completion of the immunotherapy screening period
- Cycle 1 isotretinoin should commence no sooner than 10 days following completion of radiotherapy

Cycle 2-6

- Cycles 2-6 consists of a 35 day cycle with treatment with:
  - dinutuximab beta as a continuous 10 day infusion, days 1-10, followed by
  - 14 days of isotretinoin, days 11-25
- Cycle 2 should commence no sooner than 4 days following completion of isotretinoin in cycle 1

This is detailed in Table 1 below

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Table 1: Summary table for administration of isotretinoin and dinutuximab beta

Cycle number	**1** (18 days)		**2 -6** (35 days)		
Day number	Day 1-14	Day 15-18	Day 1-10	Day 11-24	Day 25-35
Treatment with isotretinoin	✓	×	×	✓	×
Treatment with dinutuximab beta	×	×	✓	×	×

Cycle	Day	Drug	Dose	Route	Diluent & Rate	Cycle duration
1	1-14 inclusive	Isotretinoin	[a,b]160mg/m^2/day divided into two equal doses	PO	n/a	18 days
2-6	1-10 inclusive	Dinutuximab beta	[c]10mg/m^2/day	Continuous IV infusion	Continuous IV infusion over 10 days in 0.9% NaCl containing 1% human albumin	35 days
2-6	11-24 inclusive	Isotretinoin	[a,b]160mg/m^2/day divided into two equal doses	PO	n/a	35 days

[a]Patients ≤ 12kg should not receive a dose reduction and should be given a dose of 160mg/m^2
Patients > 12kg who are able to swallow isotretinoin capsules should receive a dose of 160mg/m^2
Patients ≥ 12kg who are unable to swallow isotretinoin capsules whole require an increased dose and should receive a dose of 200mg/m^2

[b]Doses will need to be rounded to the nearest 10 mg. Capsules come as 10, 20, and 40 mg sizes, and can be emptied into a high fat food such as ice cream or chocolate mousse to administer. Isotretinoin is teratogenic and should be handled with caution.

[c]Infants and children with a body weight below 12kg should be dosed according to their weight in kg instead of their body surface area (m^2) according to the known formula of 30kg = 1m^2.
In infants weighing≤ 5kg a further 1/3 dose reduction is advised.
Each dose is calculated based on the body surface area (BSA) or body weight as follows

- Patients >12kg are based on the BSA :10mg/m^2/day
- Patients ≤ 12kg are dose according to their body weight : 0.33mg/kg/day
- Patients ≤ 5kg are dose according to their body weight : 0.22mg/kg/day

ELIGIBILTY:

- Indications as above
- Age 12 months to 17 years
- High risk neuroblastoma defined as either:
  - INSS stage 2, 3, 4, and 4s with MYCN amplification, or
  - INSS stage 4 without MYCN amplification aged > 12 months at diagnosis

EXCLUSIONS:

- Hypersensitivity to dinutuximab beta, isotretinoin, or any of the excipients
- Hypersensitivity to soya, peanut
  - Following review by a paediatric allergy Consultant it may be feasible to proceed with treatment under carefully controlled conditions with resuscitation facilities available and medical and/or ITU/ HDU supervision at the discretion of the prescribing Consultant
- Acute grade 3 or 4, or extensive chronic graft-versus-host disease (GvHD)

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Paediatric Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Fasting Triglycerides
- Clinical assessment

Regular tests:
- FBC, renal and liver profile, fasting triglycerides prior to each cycle
- Clinical assessment

Disease monitoring:
Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- Prior to starting each dinutuximab treatment course, the clinical parameters as detailed in Table 2 below should be evaluated and treatment should be delayed until these values are reached
- Based on the clinician's evaluation of the severity of adverse drug reactions to dinutuximab beta, patients may undergo a dose reduction of 50% or a temporary interruption of the infusion
    - This may result in either a prolonged infusion period or a requirement to increase the infusion rate if tolerated by the patient, in order to administer the total dose

Table 2: Clinical parameters to be met before starting treatment

Dinutuximab beta	Isotretinoin
pulse oximetry > 94% on room air	Skin toxicity no greater than grade 1
absolute neutrophil count ≥ 0.5 x 10^9/L	Serum triglycerides < 500 mg/dL (5.65mmol/L)
platelet count ≥ 20 x 10^9/L	Serum calcium < 11.6 mg/dL (2.9mmol/L)
haemoglobin > 8.0 g/dL	Total bilirubin ≤ 1.5 x normal, and (SGPT) ALT ≤ 5 x normal Veno-occlusive disease if present, should be stable or improving.
ALT/AST < 5 ULN	No haematuria and/or proteinuria on urinalysis
creatinine clearance or glomerular filtration rate (GRF) > 60 mL/min/1.73 m^2	Patients with seizure disorder must be well controlled and taking anticonvulsants. CNS toxicity < grade 2.
	See table 3 below for maximum allowed serum creatinine based on age/gender

Table 3: Maximum allowed serum creatinine level allowed per age/gender prior to isotretinoin treatment

Patient Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 to < 2 years	0.6 (53 micromol/L)	0.6 (53 micromol/L)
2 to < 6 years	0.8 (71 micromol/L)	0.8 (71 micromol/L)
6 to < 10 years	1 (88 micromol/L)	1 (88 micromol/L)
10 to < 13 years	1.2 (106 micromol/L)	1.2 (106 micromol/L)
13 to < 16 years	1.5 (133 micromol/L)	1.4 (124 micromol/L)
≥ 16 years	1.7 (150 micromol/L)	1.4 (124 micromol/L)

Table 4: Dose modification table for isotreninoin therapy

Recommended daily dose	First dose reduction*	Second dose reduction*
160mg/m^2/day	120mg/m^2/day	100mg/m^2/day
*Reduce dose in succession based on the previous dose level		
If the criteria to begin the next cycle are not met by the date the cycle is due to begin, delay the cycle for one week. If the criteria are still not met, treat at 25% dose reduction (120 mg/m²/day). An additional dose reduction to 100 mg/m²/day should occur if criteria are not met within one week after due date for subsequent cycles.		

Renal and Hepatic Impairment:

Table 5: Dose modification of dinutuximab and isotretinoin in renal and hepatic impairment

Drug	Renal Impairment	Hepatic Impairment
Dinutuximab	No data available	No data available If the bilirubin increases to >3 times normal, dinutuximab beta should be withheld until the bilirubin returns to normal. Following recovery, the dinutuximab beta should be restarted at 100% dose.
Isotretinoin	Consideration could be given to dose reduction in renal impairment at the discretion of prescribing consultant **(See Table 6 for management of isotretinion induced renal toxicity**	Consideration could be given to dose reduction in hepatic impairment at the discretion of prescribing consultant

Adverse events

Table 6: Management of adverse reactions associated with dinutuximab beta and isotretinoin

Dinutuximab beta		
Adverse Reaction	**Severity**	**Treatment Modification**
Any	**Grade 1-2**	Decrease infusion rate to 50%. After resolution, resume infusion at original rate
Hypersensitivity Reaction	e.g. hypotension	Interrupt infusion and administer supportive measures. After resolution, resume infusion at original rate
Dilated pupils with sluggish light reflex +/- photophobia		Interrupt infusion. After resolution, resume infusion at 50% rate
Any	Grade≥ 3	Interrupt infusion and administer supportive measures. Resume infusion at 50% rate if ADR resolves or improves to Grade 1-2. After resolution, increase to original rate
	Recurrent	Discontinue infusion. Resume next day if adverse reaction resolves
Hypersensitivity Reaction	e.g. bronchospasm, angioedema	Interrupt infusion immediately and treat appropriately. Resume treatment for subsequent courses
Capillary leak syndrome	Grade ≥ 3	Interrupt infusion and administer supportive measures. Resume infusion at 50% rate if ADR resolves or improves to Grade 1-2
	Recurrent or grade 4	Treatment should be discontinued
Hyponatremia	Grade 4	Treatment should be discontinued

Isotretinoin		
Adverse Reaction	**Severity**	**Treatment Modification**
Any*	Grade 3 or 4	Decrease dose by 25% to 120mg/m^2/day for subsequent cycles
	Second appearance	Decrease dose by 20% to 100mg/m^2/day for subsequent cycles
	Third appearance	Discuss with clinician
Haematuria, Proteinuria, and/or hypertension		Considering withholding medication
Renal toxicity		If serum creatinine increases by > 50% in any cycle, measured GFR should be carried out prior to commencing the next cycle. If GFR is < 60 ml/min/1.73 m², then consider dose adjustment
Serum triglycerides		• If serum triglycerides are > 300 mg/dl (>3.39mmol/L) when next cycle is due, delay starting therapy for two weeks • If unresolved start patient on medical therapy for serum triglyceride reduction and begin cycle at previous isotretinoin dosage • If serum triglycerides are < 300 mg/dl (<3.39mmol/L) by time subsequent cycle is due, then continue at same dosage of isotretinoin. • If triglycerides are still > 300 mg/dl after one cycle on medical therapy, then reduce isotretinoin dosage by 25% for subsequent cycles
Localised cheilitis		Apply topical vitamin E to lips for all cycles. If this does not control symptoms sufficiently to allow sufficient oral intake, then decrease dose by 25% to 120 mg/m²/day

*Excluding: grade 3 or 4 haematologic, grade 3 hepatic, grade 3 nausea, grade 3 vomiting, or grade 3 fever

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal (**Refer to local policy).**

PREMEDICATIONS:

- Antihistamine premedication (e.g. cetirizine PO) is required daily on day 1-10 of the dinutuximab beta infusion.
- Patients should be closely monitored for anaphylaxis and allergic reactions, particularly during the first and second treatment course

OTHER SUPPORTIVE CARE:

- Apply topical vitamin E to lips for all cycles to prevent development of localised cheilitis
- Neuropathic pain usually occurs at the beginning of treatment with dinutuximab beta and premedication with analgesics, including opioids, prior to each infusion of dinutuximab beta is required.
- A triple therapy, including non-opioid analgesics (according to WHO guidelines), gabapentin and opioids, is recommended for pain treatment.
- IV opioid required when initiating therapy with dinutuximab beta. This may be weaned/titrated as appropriate during treatment. The first infusion day and course usually requires a higher dose than subsequent days and courses

Table 7: Suggested paracetamol dose for pain management during dinutuximab beta infusion (All dinutiximab infusions)

Cycle	Day	Drug	Dose	Route
All	1-10 inclusive	Paracetamol	15mg/kg (maximum 1g)	PO four times a day

Table 8: Suggested gabapentin dose for pain management during dinutuximab beta infusion (All dinutiximab infusions)

Cycle	Day	Drug	Dose	Route
All	-3	Gabapentin	10mg/kg	PO once at night
	-2	Gabapentin	10mg/kg	PO twice a day
	-1	Gabapentin	10mg/kg	Po three times day
	1-10 inclusive	Gabapentin	10mg/kg	PO three times a day
	11	Gabapentin	10mg/kg	PO twice a day
	12	Gabapentin	10mg/kg	Po once a day then stop

Table 9: Suggested morphine Infusion for pain management during dinutuximab beta infusion (First infusion)

Cycle	Day	Drug	Dose	Route	Time
1	1	*Morphine	20microgram/kg/hr	IV Infusion in 50ml glucose	Commence prior to dinutuximab infusion
		Morphine	100microgram/kg	IV bolus	Immediately prior to dinutuximab infusion

Subsequently run morphine infusion concomitantly with dinutuximab beta titrated according to pain. • Additional boli may be required during dinutuximab beta infusion if pain is uncontrolled. • In response to the patient's pain perception, it may be possible to wean off morphine over 5 days by progressively decreasing its dosing rate. • PO opioid may be prescribed as appropriate following cessation of opioid infusion • For subsequent cycles opioid analgesia should be given IV or PO at a dose determined by pain control during previous cycle. Titrate in response to the patient's pain perception
*Where patient is intolerant to morphine it may be substituted with another opioid analgesic as per Consultant decision.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

Dinutuximab

- **Hypersensitivity reactions:** Severe infusion-related reactions, including cytokine release syndrome (CRS), anaphylactic and hypersensitivity reactions, may occur despite the use of premedication. Occurrence of a severe infusion related reaction (including CRS) requires immediate discontinuation of dinutuximab beta therapy and may necessitate emergency treatment.
- **Capillary leak syndrome (CLS):** CLS is characterised by a loss of vascular tone and extravasation of plasma proteins and fluid into the extravascular space. CLS usually develops within hours after initiation of treatment, while clinical symptoms (i.e. hypotension, tachycardia) are reported to occur after 2 to 12 hours. Careful monitoring of circulatory and respiratory function is required. Treatment should be discontinued in the event of recurrent or grade 4 capillary leak syndrome (requires ventilator support)
- **Neurological disorders of the eye**: Eye disorders may occur as dinutuximab beta binds to optic nerve cells. No dose modification is necessary in the case of an impaired visual accommodation that is correctable with eye glasses, as long as this is judged to be tolerable. Treatment must be interrupted in patients who experience Grade 3 vision toxicity (i.e. subtotal vision loss per toxicity scale). In case of any eye problems, patients should be referred promptly to an ophthalmology specialist.
- **Peripheral neuropathy**: Occasional occurrences of peripheral neuropathy have been reported with dinutuximab beta EUSA. Cases of motor or sensory neuropathy lasting more than 4 days must be evaluated and noninflammatory causes, such as disease progression, infections, metabolic syndromes and concomitant medication, should be excluded. Treatment should be permanently discontinued in patients experiencing any objective prolonged weakness attributable to dinutuximab beta administration. For patients with moderate (Grade 2) neuropathy (motor with or without sensory), treatment should be interrupted and may be resumed after neurologic symptoms resolve.
- **Haematologic toxicities** Occurrence of haematologic toxicities has been reported with dinutuximab beta, such as erythropenia, thrombocytopenia or neutropenia. Grade 4 haematologic toxicities, improving to at least Grade 2 or baseline values by start of next treatment course, do not require dose modification**.**

Isotreninoin

- **Allergic Reactions:** Roaccutane® (isotreninoin) is contraindicated in patients allergic to peanut or soya. To date, there has been no significant reaction to Roaccutane® in children treated for high risk neuroblastoma. It is, however, advisable to carefully monitor any child with known peanut allergy whilst on this treatment, and to be certain that an Anapen®/ Epipen® is available for immediate use should it be required.

- **Skin and subcutaneous tissues disorders:** Exposure to intense sunlight or to UV rays should be avoided. Patients should be advised to use a skin moisturising ointment or cream and a lip balm from the start of treatment as isotretinoin is likely to cause dryness of the skin and lips.
- **Lipid Metabolism:** Serum lipids (fasting values) should be checked before treatment and monitored throughout treatment. Isotretinoin has been associated with an increase in plasma triglyceride levels.
- **Hepatobiliary disorders:** Liver enzymes should be checked before treatment, 1 month after the start of treatment, and subsequently at 3 monthly intervals unless more frequent monitoring is clinically indicated. Transient and reversible increases in liver transaminases have been reported. In many cases these changes have been within the normal range and values have returned to baseline levels during treatment. However, in the event of persistent clinically relevant elevation of transaminase levels, reduction of the dose or discontinuation of treatment should be considered.
- **Increased bone resorption:** It has been reported (rarely) that some patients treated with isotretinoin develop new areas of abnormal uptake on bone scan. This is likely to be due to increased bone resorption. If such changes occur
during the isotretinoin phase in the absence of any other evidence of tumour recurrence, discuss with primary consultant before reporting as disease progression.

DRUG INTERACTIONS:

- No dinutuximab beta interaction studies have been performed. A risk for indirect reduction of CYP activity due to higher TNF-α and IL-6 levels and, therefore, interactions with concomitantly used medicinal products, cannot be excluded.
- Due to their immunosuppressive activity, concomitant treatment with corticosteroids is not recommended within 2 weeks prior to the first treatment course until 1 week after the last treatment course with dinutuximab beta, except for life-threatening conditions.
- Vaccinations should be avoided during administration of dinutuximab beta until 10 weeks after the last treatment course, due to immune stimulation through dinutuximab beta and possible risk for rare neurological toxicities.
- Concomitant use of intravenous immunoglobulins is not recommended as they may interfere with dinutuximab beta-dependent cellular cytotoxicity
- Patients should not take vitamin A concurrently with isotretinoin due to the risk of developing hypervitaminosis A.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Dinutuximab beta	L01XC16
Isotretinoin	D10BA01

REFERENCES:

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3. Qarziba Summary of Product Characteristics. Accessed December 2018. Available at https://www.ema.europa.eu/documents/product-information/qarziba-epar-product-information_en.pdf
4. Roacutane Summary of Product Characteristics. Accessed December 2018. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2307-007-001_05122018102301.pdf

Version	Date	Amendment	Approved By
1	11/06/2019		Dr Cormac Owens

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/