

Drug Prescribing Guideline



John Hunter
Children's Hospital
CHILDREN, YOUNG PEOPLE AND FAMILIES



Health
Hunter New England
Local Health District

Isotretinoin for Paediatric Oncology

Title	Isotretinoin
Areas where Guideline applicable e.g. ITU, Haematology, Ward	Paediatric Oncology
Areas where Guideline not applicable	All areas except Paediatric Oncology
Keywords	Isotretinoin, cis-retinoic acid, Roaccutane [®] , 13-cis-RA, oncology, paediatric oncology, neuroblastoma, high risk neuroblastoma
Authorised Prescribers:	Paediatric Oncologists
Indication for use	Improve event free survival in patients with High Risk Neuroblastoma (part of treatment plan)
Clinical condition Patient selection: Inclusion criteria (list investigations necessary and relevant results)	High Risk Neuroblastoma Established diagnosis of High Risk Neuroblastoma according to International Neuroblastoma Staging System (INSS). Females of childbearing potential must have a negative pregnancy test. Patients of childbearing potential must agree to use an effective birth control method. Female patients who are lactating must agree to stop breast-feeding.
Contra-indications	Pregnancy, lactation
Precautions	Women of childbearing age – adequate contraception must be used before, during and for 1 month after, treatment, because birth defects can occur during this time. Capsules contain soya oil; therefore caution should be taken with patients allergic to peanut or soya.
Proposed Place in Therapy State whether drug to be used as first, second or third line. Where not first line describe therapies to be used first. (Consider using algorithm)	Part of first line treatment for High Risk Neuroblastoma Drug used in final phase of HRNBL1.5/SIOPEN treatment protocol (Differentiation Therapy)
If part of combination therapy then list other drugs	Used with monoclonal antibody Ch14.18/CHO (GD2 receptor antibody)
Dosage	Orally 160 mg/m ² /day in 2 divided doses (rounded to the nearest 10 mg), for the first 14 days of each 28 day cycle, for a total of 6 cycles. No dose adjustment required for children < 12 kg. Dose modifications: (a) A dose reduction of 25% (to 120 mg/m ² /day) for subsequent cycles should be made for the occurrence of any grade 3 or 4 CTC toxicity. EXCLUDING: Grade 3 or 4 haematological, grade 3 hepatic, grade 3 nausea, grade 3 vomiting or grade 3 fever. If the same grade 3 or 4 toxicity recurs after a 25% dose reduction, then decrease the dose by another 20% (to 100 mg/m ² /day). If the same grade 3 or 4 toxicity recurs after two dose reductions, then discuss with study co-ordinator before continuing further therapy.

	<p>(b) It has been reported (rarely) that some patients treated with isotretinoin (13-cis-RA) develop new areas of abnormal uptake on bone scan. This is likely to be due to increased bone reabsorption. If such changes occur during the isotretinoin (13-cis-RA) phase in the absence of any other evidence of tumour recurrence, discuss with study co-ordinator before reporting as disease progression.</p> <p>(c) 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.</p> <p>(d) If serum creatinine increases by > 50% in any cycle, eGFR should be estimated prior to commencing the next cycle. If eGFR is < 50 mL/min/1.73 m², then call the study coordinator for dose adjustment.</p> <p>(e) For localised cheilitis, apply topical vitamin E to lips for subsequent cycles. If this does not control symptoms sufficiently to allow sufficient oral intake, then decrease dose by 25% to 120 mg/m²/day.</p> <p>(f) If serum triglycerides are > 3.39 mmol/L when next cycle is due, delay starting therapy for two weeks. If still > 3.39 mmol/L, then start patient on medical therapy for serum triglyceride reduction and begin cycle at previous isotretinoin (13-cis-RA) dosage. If serum triglycerides are < 3.39 mmol/L by time subsequent cycle is due, then continue at same dosage isotretinoin (13-cis-RA). If triglycerides are still > 3.39 mmol/L after one cycle on medical therapy, then reduce isotretinoin (13-cis-RA) dosage by 25% for subsequent cycles.</p>
<p>Duration of therapy</p>	<p>To be taken for the first 14 days of each 28 day cycle, for a total of 6 cycles.</p> <p>To be commenced after completion of local irradiation on Day 90 post peripheral blood stem cell rescue, and certainly no later than by Day 120 post peripheral blood stem cell rescue.</p>
<p>Administration instructions</p>	<p>Capsule to be given orally.</p> <p>To be swallowed whole, with or soon after food or milk.</p> <p>If patient unable to swallow capsule(s) whole: Don mask, gloves and eye glasses to pierce capsule and squeeze the contents into milk or a high fat food (i.e. yoghurt). Give dose ensuring that all of the food or milk is given.</p> <p>Alternatively, remove the plunger from a small (3 mL) syringe and place capsule inside the barrel of the syringe. Replace the plunger of the syringe so that it is pressed against the capsule. Using another syringe with a needle attached, carefully pierce the capsule through the tip of the syringe containing the capsule. Withdraw the contents of the capsule and add capsule contents to water. Give immediately as capsule contents are unstable, preferably ensuring that the dose is given with or soon after milk or food. If administering into a feeding tube, flush tube well after giving dose. Discard needles appropriately.</p> <p>Wear mask, gloves and eye glasses if piercing capsules.</p> <p>Do not handle capsule contents if pregnant or intending to become pregnant, unless wearing appropriate PPE.</p>

<p>Starting/Monitoring requirements</p>	<p>Each isotretinoin cycle only to be started when there has been approval ('go-ahead') from the Oncologist. Patient must meet the following starting criteria (if starting criteria not met, see Dosage and Management of Complications sections):</p> <ul style="list-style-type: none"> • Total bilirubin $\leq 1.5 \times$ normal and ALT $\leq 5 \times$ normal. Veno-occlusive disease, if present, should be stable or improving. • Skin toxicity no greater than grade 1 • Serum triglycerides < 5.65 mmol/L • No haematuria and/or proteinuria on urinalysis • Serum calcium < 2.9 mmol/L • Serum creatinine based on age/gender as follows: <p>Age Maximum Serum Creatinine (micromol/L)</p> <table border="1" data-bbox="742 678 1284 954"> <thead> <tr> <th></th> <th>Male</th> <th>Female</th> </tr> </thead> <tbody> <tr> <td>1 month to < 6 months</td> <td>35</td> <td>35</td> </tr> <tr> <td>6 months to < 1 year</td> <td>44</td> <td>44</td> </tr> <tr> <td>1 to < 2 years</td> <td>53</td> <td>53</td> </tr> <tr> <td>2 to < 6 years</td> <td>71</td> <td>71</td> </tr> <tr> <td>6 to < 10 years</td> <td>88</td> <td>88</td> </tr> <tr> <td>10 to < 13 years</td> <td>106</td> <td>106</td> </tr> <tr> <td>13 to < 16 years</td> <td>133</td> <td>124</td> </tr> <tr> <td>≥ 16 years</td> <td>150</td> <td>124</td> </tr> </tbody> </table>		Male	Female	1 month to < 6 months	35	35	6 months to < 1 year	44	44	1 to < 2 years	53	53	2 to < 6 years	71	71	6 to < 10 years	88	88	10 to < 13 years	106	106	13 to < 16 years	133	124	≥ 16 years	150	124
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<p>Safety</p>	<p>Phase I study has shown Isotretinoin to be well tolerated in children with Stage 4 neuroblastoma. Toxicity that occurred was mild and consisted of cheilitis, dry skin and hypertriglyceridaemia. Intermittent therapy (2 weeks on and 2 weeks off) is used to minimise incidence of toxicity. All patients are provided with verbal and written information regarding adverse-effects and their management.</p> <p>Common side effects include acne flare which occurs usually during the first few weeks of treatment.</p> <p>Paronychia, Stevens-Johnson syndrome, toxic epidermal necrolysis, colitis, neutropenia, anaemia and thrombocytopenia have also been reported.</p>																											
<p>Effectiveness (state objective criteria)</p>	<p>Efficacy measured by event free survival and overall survival. Trials have shown isotretinoin to be effective in inducing neuroblastoma cell differentiation and apoptosis. In neuroblastoma, use of isotretinoin (in conjunction with other therapies) has been shown to increase the survival rate 3 years after randomisation from $29\% \pm 5\%$ to $46\% \pm 6\%$. See study paper for further information and subgroup analyses.</p>																											
<p>Management of complications</p>	<p>If complications occur, the dose may be decreased or the cycle delayed (see Dosage section)</p> <p>Skin dryness and cheilitis – apply vitamin E cream to lips and skin as often as needed. Decrease isotretinoin dose if cheilitis affects oral intake.</p> <p>Skin sensitivity – avoid direct exposure to sunlight while on treatment. Avoid exposure to vitamin A products while on treatment.</p> <p>Serum creatinine – $> 50\%$ increase; decrease isotretinoin dose.</p> <p>Haematuria, proteinuria, and/or hypertension – withhold medication and contact study co-ordinator.</p>																											

	Hypercalcaemia – delay next cycle, aggressive intravenous hydration. Hypertriglyceridaemia – if > 3.39 mmol/L, delay cycle (see Dosage section)
Important Drug Interactions	Vitamin A supplementation – risk of vitamin A toxicity Tetracyclines, minocycline, doxycycline – risk of pseudotumor cerebri (benign intracranial hypertension) Methotrexate – increased risk of hepatotoxicity Hormonal contraceptives – risk of reduced contraceptive efficacy, recommend using two forms of contraception or abstinence while on isotretinoin.
Basis of Guideline: (including sources of evidence, references)	<ul style="list-style-type: none"> • HRNBL1.5/SIOPEN Clinical Trial • Society of Hospital Pharmacists Australia: Don't Rush To Crush, 1st Edition* • MIMS Online* • Micromedex* • Australian Medicines Handbook* • *Available via CIAP
Groups consulted in development of this guideline	Paediatric Oncology, Pharmacy, KQUMC, JHCH CPGAG

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