# Bexarotene

## INDICATION

Cutaneous T-cell lymphoma

## TREATMENT INTENT

Disease modification

## PRE-ASSESSMENT

1. Ensure histology is confirmed prior to administration of chemotherapy and document in notes.
2. Record stage of disease – By clinical examination. Consider performing CT NCAP / PET-CT to look for systemic involvement. Also consider flow cytometry of peripheral blood.
3. Blood tests - FBC, DAT, U&Es, LDH, ESR, fasting lipid profile, thyroid function tests, CK, urate, calcium, magnesium, creatinine, LFTs, glucose, Igs, $\beta_2$ miin croglobulin, hepatitis B core antibody and hepatitis B surface Ag, hepatitis C antibody, EBV, CMV, VZV, HIV 1+2 after consent, group and save. Consider flow cytometry.
4. Urine pregnancy test - before cycle 1 of each new chemotherapy for women of child-bearing age unless they are post-menopausal, have been sterilised or undergone a hysterectomy.
5. ECG +/- Echo - *if clinically indicated*.
6. Record performance status (WHO/ECOG).
7. Record height and weight.
8. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent on the day of treatment.
9. Fertility - it is very important the patient understands the potential risk of infertility, all patients should be offered fertility advice by referring to the Oxford Fertility Unit.
10. Hydration - *in patients with bulky disease* pre-hydrate with sodium chloride 0.9% 1 litre over 4-6 hours. Patients at high risk of tumour lysis refer to tumour lysis protocol.
11. Consider dental assessment / Advise dental check is carried out by patient's own dental practitioner before treatment starts.
12. For patients prescribed oral chemotherapy, ensure pre-chemotherapy counselling in line with NPSA recommendation and chemotherapy measures.
13. Patients on simvastatin or gemfibrozil should be switched to equivalent doses of alternative preferred lipid lowering drugs (due to drug interactions)- see regimen and drug interactions section)
14. Treatment should be agreed in the relevant MDT.
15. Contraception in males and females: women of childbearing potential must use adequate birth-control measures when bexarotene is used. A negative, sensitive, pregnancy test (e.g. serum beta-human chorionic gonadotropin, beta-HCG) should be obtained within one week prior to bexarotene therapy. Effective contraception must be used from the time of the negative pregnancy test through the initiation of therapy, during therapy and for at least one month following discontinuation of therapy. Whenever contraception is required, it is recommended that two reliable forms of contraception be used simultaneously. Bexarotene can potentially induce metabolic enzymes and thereby theoretically reduce the efficacy of oestroprogestative contraceptives Thus, if treatment with bexarotene is intended in a woman with childbearing

potential, a reliable, non-hormonal contraceptive method is also recommended. Male patients with sexual partners who are pregnant, possibly pregnant, or may potentially become pregnant must use condoms during sexual intercourse while taking bexarotene and for at least one month after the last dose.

## DRUG REGIMEN AND CYCLE FREQUENCY

| | |
|---|---|
| **Week 1** | **FENOFIBRATE** 160mg OD PO (on going dosing)<br>(or Atorvastatin 20mg OD PO) |
| **Weeks 2-5**<br>**Induction** | **BEXAROTENE** 150mg/m$^2$ OD PO, **with food**<br>Levothyroxine 25-50 micrograms OD PO<br>(25microgram if history of cardiovascular disease) |
| **Weeks 6**<br>**Maintenance** | **BEXAROTENE** 300mg/m$^2$ OD PO (on going dosing) |

Note: for patients with unstable lipids or other dose related adverse events, recommended to increase bexarotene dose by 75 mg (one capsule) per day, every 2-4 weeks during the start of the maintenance phase, until dose of 300mg/m$^2$ reached.

Treatment is continuous for responders and those with stable disease until progression or unacceptable toxicity. Responses may take up to 6 months

## DOSE MODIFICATIONS

### Haematological toxicity:

| Blood rests | Bexarotene dose |
|---|---|
| Neutrophils > 0.8x10$^9$/L<br>Neutrophils 0.5-0.8x10$^9$/L<br>Neutrophils < 0.5x10$^9$/L | 100%<br>Dose reduce to 200mg/m$^2$<br>Delay dose |

### Hyperlipidaemia:

Aim for Total Cholesterol (TC) levels < 7mmol/L, optimally keep LDL-Cholesterol <2mmol/L and TC<4mmol/L.
Aim for triglyceride level < 5.5 mmol/L (<3.5mmol/L in patients with known cardiovascular disease) (CVD)

| Fasting triglyceride (mmol/L) | Bexarotene dose |
|---|---|
| < 5.5<br>> 7.5 (> 5.5 in patients with CVD)<br>> 10 | 100%<br>Dose reduce to 200mg/m$^2$<br>Delay until under control (check amylase) |

NB If > 5.5 add in Atorvastatin 20-80 mg nocte – see under concurrent medication.

**Liver function tests**

| Bilirubin, ALT and / or AST | Bexarotene dose |
|---|---|
| > 3x upper limit of normal for any of the tests | Delay dose until resolved |

**Thyroid function tests – aim fT4 upper third normal range**

| TSH, fT4, fT3 | Bexarotene dose |
|---|---|
| fT4 below lower limit of normal | No change in dose but increase dose of Thyroxine by 25mcg increments up to max 225mcg (see under concurrent medication) |

## INVESTIGATIONS

- FBC, U&E & LFTs weekly during the first month until stabilized then monthly.
- TSH, fT4, fT3 weekly until stabilized then monthly (Note: bexarotene causes a predictable repression in TSH and so fT3 and fT4 must be used to monitor thyroid hormone status and adequacy of replacement).
- Fasting glucose and triglycerides and cholesterol weekly until stabilized then monthly.
- Two-weekly blood testing during dose escalation.

## CONCURRENT MEDICATION

Thyroxine to treat reversible hypothyroidism:

- Maintain fT4 within upper third of local laboratory values
- Gradually titrate dose of levothyroxine every 2 weeks in 25-50 microgram increments
- Maximum dose of thyroxine is 225 micrograms (higher doses provide no additional benefit)
- If no prior hypothyroidism, levothyroxine can stop immediately on cessation of bexarotene due to long half-life of levothyroxine

Fenofibrate should be started in all patients who commence bexarotene unless there is a contraindication. If triglycerides remain > 5.5 (>3.5 if cardiovascular disease) add in Atorvastatin 20-80mg nocte. Commence 20mg and titrate up every 2 weeks to a maximum dose of 80mg. If triglycerides remain elevated, discuss with a lipidologist.

Note: when stopping bexarotene, lipid lowering agents should be stopped immediately, or reduced to pre-bexarotene doses. If the drug is being held due to toxicity, lipid lowering agents can continue (whereas thyroxine should be stopped and re-started when bexarotene is re-started).

Atorvastatin 20-80mg: aim for total cholesterol < 7 mmol/L. If cholesterol remains elevated, discuss with lipidologist.

If fasting blood glucose >6.5 consider starting metformin.

## DRUG INTERACTIONS

(Refer to the product SmPC for full details)

Bexarotene is metabolised by CYP3A4. CYP3A4 inducers (carbamazepine, efavirenz, phenytoin, phenobarbital, dexamethasone, rifampicin, St John's wort etc.) may reduce the efficacy of bexarotene. CYP3A4 inhibitors (Amiodarone, ciprofloxacin, clarithromycin, diltiazem, erythromycin, fluconazole, grapefruit juice, itraconazole, ritonavir, verapamil, voriconazole etc.) may increase the toxicity of bexarotene.

Simvastatin and gemfiprozil co-administeration with bexarotene should be avoided due to interactions. Caution with atorvastatin.

Vitamin A supplementation should also be avoided and limited to ≤15 000 IU/day.

Bexarotene may potentially enhance the action of insulin and agents enhancing insulin secretion (e.g sulfonylureas), or insulin sensitizers (e.g. thiazolidinediones) resulting in hypoglycaemia. Caution should be exercised in case of co-administration.

Bexarotene can potentially induce metabolic enzymes and thereby theoretically reduce the efficacy of oestroprogestative contraceptives, women with childbearing potential, must use two reliable forms of contraception be used simultaneously, including a non-hormonal contraceptive method.

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**EMETIC RISK**

Low

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**ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS**

Hypothyroidism
Hyperlipidaemia: Patients should receive lifestyle and dietary advise to minimize modifiable risk factors i.e. low fat diet, limit alcohol consumption within the UK recommendations, exercise to lower triglycerides.
Pancreatitis
LFTs abnormalities
Photosensitivity: advise patients to minimize exposure to sunlight and artificial UV radiation; high factor sunscreens are recommended.
Leucopenia
Anaemia
Psychiatric disorders- depression, anxiety, and mood changes. Patients should be monitored for signs of depression and referred for appropriate treatment if necessary.
Lens opacity

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**TREATMENT RELATED MORTALITY:**

< 1%

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| Name | Revision | Date | Version | Review date |
|---|---|---|---|---|
| Sara Castro (Advanced Haematology Pharmacist) | Annual Protocol Review | May 2021 | 1.4 | May 2023 |

**REFERENCES**

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4. Scarisbrick JJ, Morris S, Azurdia R, Illidge T, Parry E, Graham-Brown R, Cowan R, Gallop-Evans E, Wachsmuth R, Eagle M, Wierzbicki AS, Soran H,Whittaker S, Wain EM. U.K. consensus statement on safe clinical prescribing of bexarotene for patients with cutaneous T-cell lymphoma. Br J Dermatol 2013 Jan;168(1):192-200.