Shared Care Guideline – GP monitoring bloods only (no prescribing required)
Bosentan for digital ulcers in systemic sclerosis

Executive Summary

- Bosentan is used for digital ulcers in adult patients with scleroderma.
- Bosentan reduces the number of new finger and toe ulcers that appear.
- Bosentan will be initiated and prescribed by Hospital Specialists.
- **Monitoring of liver function tests and haemoglobin by GPs is required.**
- Bosentan has multiple drug interactions.
- Pregnancy and breastfeeding should be avoided during bosentan therapy.
- The responsibilities of the hospital specialist, GP and patient for this Shared Care Guideline can be found within this document here

Sharing of care depends on communication between the specialist, GP and the patient or their parent/carer. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. The doctor/healthcare professional who prescribes the medication has the clinical responsibility for the drug and the consequences of its use. Further information about the general responsibilities of the hospital specialist and GP can be found here

1. Scope

Monitoring by General Practitioners

2. Aim

To provide guidance in the use of bosentan for digital ulcers.

3. Introduction

Bosentan is an endothelin receptor antagonist, which blocks a naturally occurring hormone called endothelin-1 (ET-1), which causes blood vessels to narrow. It therefore causes blood vessels to expand and belongs to the class of medicines called “endothelin receptor antagonists”.
Bosentan is used for digital ulcers (sores on the fingers and toes) in adult patients with scleroderma. Bosentan reduces the number of new finger and toe ulcers that appear.

4. Abbreviations

- AST - Aspartate aminotransferases
- ALT - Alanine aminotransferases
- BNF – British National Formulary
- CTD – Connective Tissue Disease
- ET–1 – Endothelin-1
- GP – General Practitioner
- Hb - Haemoglobin
- LFT – Liver function tests
- ULN – Upper Limit of Normal

5. Dose and Administration

Bosentan is initiated at a dose of 62.5mg orally twice daily (morning and evening) for four weeks. After this 4 week period, if this dose is tolerated, it is increased to 125 mg orally twice a day.

Tablets are available as 62.5mg and 125mg strengths. They should be taken with water may be taken with or without food.

Further information can be found in the Summary of Product Characteristics

6. Adverse Effects

Very common (≥ 1 in 10)

- Oedema, fluid retention
- Abnormal LFTs
- Headache

Common (≥ 1 in 100 and < 1 in 10)

- Anaemia, haemoglobin decrease
- Hypersensitivity reactions (including dermatitis, pruritus and rash
- Syncope
- Palpitations
- Flushing
- Hypotension
- Nasal Congestion
- Gastro oesophageal reflux disease
- Diarrhoea
- Erythema

Uncommon (≥ 1 in 1000 and < 1 in 100)

- Thrombocytopenia
- Neutropenia
- Leukopenia

Rare (≥ 1 in 10000 and < 1 in 1000)

- Anaphylaxis and/or angioedema
- Liver cirrhosis, liver failure

Further information can be found in the Summary of Product Characteristics.

7. Cautions

- Breastfeeding – at the time of publication no information is available on the safety of bosentan in breastfeeding. The manufacturer advises to avoid. Up to date information should be obtained from Medicines Information on a case by case basis.
- Bosentan should only be initiated if the systemic systolic blood pressure is higher than 85 mmHg.

Further information can be found in the Summary of Product Characteristics.

8. Contraindications

- Pregnancy
- Women of child-bearing potential who are not using reliable methods of contraception (hormonal contraception not considered effective)
- Hypersensitivity to the active substance or to any of the excipients
- Moderate to severe hepatic impairment, i.e. Child-Pugh class B or C
- Baseline values of AST and/or ALT greater than 3 times the upper limit of normal
- Concomitant use of ciclosporin
- Severe haematological impairment or profound deterioration

Further information can be found in the Summary of Product Characteristics.

Interactions

For reference, a list of *commonly* prescribed drugs that have the potential for *moderate/severe* clinically significant interactions with bosentan have been listed below.
However, bosentan has multiple drug interactions, many of which are significant/severe, that are not listed here.
The Summary of Product Characteristics and the BNF should be consulted before starting any new drug or modifying existing drug therapy. Further information may be obtained from Medicines Information.

- Methotrexate (case reports)
- Calcium channel blockers
- Carbamazepine
- Ciclosporin
- Fluconazole
- Glibenclamide
- Hormonal contraceptives including progesterone only and combined
- Methadone
- Phenytoin
- Phenobarital
- St John's Wort
- Warfarin

9. Monitoring Standards & Actions to take in the event of abnormal test results/symptoms

Test	Monitoring schedule - see Section 10 for full details
Pregnancy	• Initiation - Hospital specialist
Blood pressure	• Initiation - Hospital specialist

Haemoglobin	• Initiation - Hospital specialist • 2 weeks after initiation - Hospital Specialist (or GP on request) • 2 weeks after any dose escalation - Hospital Specialist (or GP on request) • Monthly for the first 4 months, then every 3 months - Hospital Specialist (or GP on request) •
LFTs	• Initiation - Hospital specialist • 2 weeks after initiation - Hospital Specialist (or GP on request) • 2 weeks after any dose escalation - Hospital Specialist (or GP on request) • Monthly for duration of treatment - Hospital Specialist (or GP on request)
Photography	• Initiation - Hospital Specialist • Every 6 months – Hospital Specialist

ALT/AST levels	**Action for GP**	**Action for Hospital Specialist**
> 3 and ≤ 5 × ULN	• Call the Specialist Nurse (CTD) Advice Line (01223 596441) or otherwise making contact with the Rheumatology Department.	• Confirm result by a second liver test. • Decide on an individual basis to continue, possibly at a reduced dose, or to stop. • Monitor ALT/AST at least every 2 weeks. • If levels return to pre-treatment values continuing or re-introduction may be considered (consider hepatology opinion). • After reintroduction ALT/AST must be checked in 3 days and after a further 2 weeks, and thereafter according to the usual recommendations.
> 5 and ≤ 8 × ULN	• Advise patient to stop bosentan. • Call the Specialist Nurse (CTD) Advice Line (01223 596441) or otherwise making contact with the Rheumatology Department.	• Confirm result by a second liver test. • If confirmed, treatment should be stopped. • Monitor ALT/AST levels at least every 2 weeks. • If levels return to pre-treatment values re-introduction may be considered (consider hepatology opinion). • After reintroduction ALT/AST must be checked in 3 days and after a further 2 weeks, and thereafter according to the usual recommendations.
> 8 × ULN	• Advise patient to stop bosentan. • Call the Specialist Nurse (CTD) Advice Line (01223 596441) or otherwise making contact with the Rheumatology Department.	• Treatment must be stopped and re-introduction is not to be considered.
Patient has clinical symptoms suggestive of liver injury	**Action for GP**	**Action for Hospital Specialist**
e.g. nausea, vomiting, fever, abdominal pain, jaundice, unusual lethargy or fatigue, flu-like syndrome (arthralgia, myalgia, fever)	• Advise patient to stop bosentan. • Recheck ALT/AST. • Call the Specialist Nurse (CTD) Advice Line (01223 596441) or otherwise making contact with the Rheumatology Department.	• If liver injury is confirmed treatment must be stopped and re-introduction is not to be considered.
Haemoglobin	**Action for GP**	**Action for Hospital Specialist**
Clinically relevant decrease in haemoglobin concentration (Hb<100 g/L or a drop	• Call the Specialist Nurse (CTD) Advice Line (01223 596441) or otherwise making contact with the Rheumatology Department. • Consider further evaluation and	• Decide on an individual basis to continue, possibly at a reduced dose, or to stop.

of more than 20 g/L)	investigation to determine the causes other than bosentan and need for specific treatment	

10. Shared Care Responsibilities

- **Hospital specialist/Specialist Nurse (CTD):**
- Prescribe bosentan.
- Check baseline LFTs, haemoglobin and blood pressure and confirm a negative pregnancy test (the latter, if applicable).
- Document/record initiation of bosentan appropriately in the patient's Epic record.
- Counsel the patient on the use of bosentan including dose, monitoring requirements (including importance of blood tests), need for effective contraception (hormonal contraception not considered effective) and side effects.
- Provide a Blood Monitoring booklet and record the date of initiating bosentan. Ensure that the patient understands that they should carry the book at all times. Update the Blood Monitoring booklet at scheduled appointments.
- Send a letter to the GP requesting shared care for the patient, to start after the patient achieves a stable dose – usually after 6 weeks.
- Inform the patient to make an appointment for their first monitoring blood test, at their GP surgery, 8 weeks after starting bosentan, unless otherwise advised.
- Arrange a further check of LFT and haemoglobin 2 weeks after initiation and 2 weeks after dose escalation. Note that this will be performed at CUH if the patient lives locally. However, it may be arranged at the GP surgery (following discussion with the GP) if the patient has a significant travelling distance to CUH.
- Check blood results from 2 weeks and notify patient when to escalate dose, usually 4 weeks after initiation (after reviewing the blood test performed 2 weeks after initiation).
- Inform the GP after each clinic attendance if there is any change to treatment or monitoring.
- Attempt to contact patients who do not attend clinic appointments and inform GP of outcome. If it is impossible to make contact with the patient, send a letter to explain that no further bosentan will be prescribed until further review.
- Monitoring response to the therapy/checking for toxicity at clinic appointments every 6 months. An additional telephone consultation will be conducted between clinic appointments with the CTD Nurse.
- The decision to prescribe bosentan will be reviewed every 6 months and no further prescriptions will be issued if the patient has not had monitoring tests done, with results in the notes, within 2 months of the prescribing date.
- To provide any advice to the patient/carer/GP when requested.

- **General Practitioner:**
  - Agreement to shared care guideline by the GP.
  - Blood monitoring (see Section 9):
    - Perform LFTs monthly for duration of treatment and, upon request from the Hospital Specialist, 2 weeks after dose increases.
    - Perform haemoglobin monthly for the first 4 months, then every 3 months.
    - Review the results and, if required, contact the CTD Nurse Advice Line.
    - Inform the Hospital Specialist if the patient does not attend for blood tests.
    - Complete blood monitoring details in the Blood Monitoring booklet or provide information to be included within it and ensure that patient understands they should carry the book at all times.

- Report any adverse events to the hospital specialist, where appropriate.
- Request advice from the hospital specialist when necessary.

- **Patient or parent/carer:**
- Arrange the first monitoring appointment with their GP. This will usually be 8 weeks after bosentan initiation, unless other arrangements have been made with the GP.
- Keep the Blood Monitoring booklet up to date.
- Patients must bring their Blood Monitoring booklet to all appointments or consultations with a health professional.
- Report to the hospital specialist or GP if they do not have a clear understanding of their treatment or wish to discuss any concerns relating to their treatment.
- Patients must not exceed the recommended dose.
- Patients must attend their scheduled clinic and blood test appointments (where relevant).
- Must inform other clinical staff that they are receiving treatment.
- Report any adverse effects to the hospital specialist or GP.
- Women of childbearing age should use effective contraception required during bosentan therapy (hormonal contraception, including oral, injectable, transdermal or implantable forms, is not considered effective). They should contact the GP or specialist immediately if they suspect they could be pregnant and conduct monthly pregnancy tests if they are sexually active.

11. Contact numbers for advice and support

Cambridge University Hosiptals		
Specialist	**Post**	**Telephone**
Dr FC Hall	Consultant rheumatologist	01223 256883
Dr N Jordan	Consultant rheumatologist	01223 256883
Teresa Del Sordo	CTD Specialist Nurse	01223 596441
	Patients' Medicines Helpline/Medicines Information	01223 217502

12. Equality and Diversity Statement

This document complies with the Cambridge University Hospitals' service Equality and Diversity statement.

13. Disclaimer

It is your responsibility to check that this printed out copy is the most recent issue of this document.

14. Document Management

Document ratification and history	
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The information contained in this guideline is issued on the understanding that it is accurate based on the resources at the time of issue. For further information please refer to the most recent Summary of Product Characteristics.