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

Executive Summary

- Bosentan is used for digital ulcers in adult patients with systemic sclerosis
- 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.

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.

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 systemic sclerosis. 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

CUH	Cambridge University Hospitals NHS Foundation Trust
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 four 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 ash may be taken with or without food.

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

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 85mmHg.

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, ie Child-Pugh class B or C
- Baseline values of AST and/or ALT greater than three times the upper limit of normal
- Concomitant use of ciclosporin
- Acute porphyria

9. Interactions

Please note that bosentan is an inducer of CYP3A4 and CYP2C9 isoenzymes, which can decrease the effectiveness of drugs that are metabolised by them.

We have listed the most clinically significant interactions below. If you have any queries regarding other drug interactions listed in the Summary of Product Characteristics or BNF, please contact the specialist team or CUH medicines information department by emailing cuh.medicinesinformation@nhs.net or calling 01223 217502 for further support.

- Hormonal contraceptives including progesterone only and combined – ***Bosentan decreases the exposure to combined and progesterone only contraceptives, these alone are not considered an effective form of contraception in those taking bosentan.***
- Ciclosporin – *Increased exposure to bosentan, concomitant use contraindicated.*
- Fluconazole – *Use together not recommended - increased bosentan exposure.*
- Glibenclamide – *Use together not recommended - increased risk of liver toxicity and reduced exposure to both drugs*
- Rifampicin – *Use together not recommended*
- Warfarin – *Reduction in warfarin exposure*

Further information about dose and administration, adverse effects, cautions, contraindications and interactions can be found in the Summary of Product Characteristics.

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

Test	Monitoring schedule - see Section 11 for full details
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

Test results / symptoms	Action for GP	Action for hospital specialist
ALT/AST levels > 3 and ≤ 5 × ULN	• Call the specialist nurse (CTD) Advice Line (01223 596441)	• 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 within 2 weeks, and thereafter according to the usual recommendations.

Test results / symptoms	Action for GP	Action for hospital specialist
ALT/AST levels > 5 and ≤ 8 × ULN	• Advise patient to stop bosentan. • Call the specialist nurse (CTD) advice line (01223 596441)	• 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.
ALT/AST levels > 8 × ULN	• Advise patient to stop bosentan. • Call the specialist nurse (CTD) advice line (01223 596441)	• Treatment must be stopped and re-introduction is not to be considered.
Patient has clinical symptoms suggestive of liver injury eg nausea, vomiting, fever, abdominal pain, jaundice	• Advise patient to stop bosentan. • Recheck ALT/AST. • Call the specialist nurse (CTD) advice line (01223 596441)	If liver injury is confirmed treatment must be stopped and re-introduction is not to be considered.
Haemoglobin Clinically relevant decrease in haemoglobin concentration (Hb<100 g/L)	• Call the specialist nurse (CTD) advice line (01223 596441) • Consider further evaluation and investigation to determine the causes other than bosentan and need for specific treatment	• Decide on an individual basis to continue, possibly at a reduced dose, or to stop.

11. Shared Care Responsibilities

a. Hospital specialist:

- Prescribe bosentan.
- Check baseline LFTs, haemoglobin and blood pressure and confirm a negative pregnancy test (the latter, if applicable).
- Document/ record initiation of bosentan, and whether monitoring should include serial pregnancy tests, appropriately in the patient's Epic record.
- Counsel the patient on the use of bosentan including dose, monitoring requirements (including importance of blood tests), and, **where appropriate, the need for effective contraception** (hormonal contraception not considered effective) and side effects. Where female patients are of childbearing age and are sexually active, use of either copper coil (1:100 pregnancy rate) or vaginal ring (9:100 pregnancy rate) provide similar or better protection than use of the combined or mini pill (8:100 pregnancy rate in women not taking bosentan).
- Provide a monitoring plan and record the date of initiating bosentan. Where blood tests are being performed by GPs, provide forms for future blood tests to cover the period until the next review. The blood tests will then be taken by the GP and returned to CUH. Review monitoring blood results at scheduled appointments and at interim time-points, if there are specific concerns.
- 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.
- Inform GP of patients who do not attend clinic appointments and advise regarding arrangements for further follow up.
- 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.

b. General Practitioner:

- Agreement to shared care guideline by the GP.
- Blood monitoring (see section 10):
- Perform blood tests for which the hospital has provided request forms.
- 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.
- Report any adverse events to the hospital specialist, where appropriate.
- Request advice from the hospital specialist when necessary.

c. 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.
- 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 contraption, 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.
- Women of childbearing age should conduct monthly pregnancy tests if they are sexually active.

12. Contact numbers for advice and support

Cambridge University Hospitals NHS Foundation Trust

Specialist	Post	Telephone
Dr FC Hall	Consultant Rheumatologist	Mobile via switchboard
Dr C Stober	Consultant Rheumatologist	Mobile via switchboard
Teresa Del Sordo	CTD Specialist Nurse	01223 596441
	Patients' Medicines Helpline/ Medicines Information	01223 217502 or cuh.medicinesinformation@nhs.net

13. Equality and Diversity Statement

This document complies with the Cambridge University Hospitals NHS Foundation Trust service Equality and Diversity statement.

14. Disclaimer

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

15. Document Management

Ratification Process	Details
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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.

Bosentan for digital ulcers in systemic sclerosis - Template Letter

{GP ADDRESS}

Dear Dr,

{PATIENT DETAILS}

Your patient was seen on **{Insert date}** with a diagnosis of systemic sclerosis. He/she has digital ulcer disease. I have therefore initiated Bosentan tablets and am writing to ask you to participate in the shared care blood monitoring for this patient.

This medication and indication has been accepted as suitable for shared care monitoring by the Cambridgeshire and Peterborough Integrated Care System. I agree to the secondary care responsibilities set out in the shared care agreement for this medication. I am therefore requesting your agreement to share the care of this patient.

Medication name: **Bosentan tablets**

Current dose: {insert dose}

Date medication started: {Insert date}

Next Blood Test due: {Insert date}

Last bloods and blood pressure were taken on {Insert date} and these show {comment on result}. The latest results are attached below.

{Insert the latest blood test results. Includes BP, Renal function, haemoglobin and LFTs}

I confirm I have explained to the patient: the risks and benefits of treatment, the baseline tests conducted and the need for monitoring, how monitoring will be arranged, and the roles of the consultant/nurse specialist, GP and the patient in shared care.

I confirm the patient has understood and is satisfied with this shared care arrangement.

Yours sincerely

{Consultant/ Practitioner name}