North Central London
Joint Formulary Committee

Cholestatic pruritus treatment pathway

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Document control

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Contents

1. Target audience

This guidance is made for all clinicians involved with the initiation and ongoing prescribing of medications for cholestatic itch across Primary, Secondary and Tertiary care.

2. Purpose

The purpose of this document is to provide information on medications used in the management of cholestatic itch and outline their use in the treatment pathway for adult patients.

The information is also intended to help GPs when considering requests to continue prescribing of these medications in adult patients receiving stable doses for whom treatment has been started by a Hepatologist in secondary and tertiary care.

3. Introduction

Primary Biliary Cholangitis (PBC) and Primary Sclerosing Cholangitis (PSC) are rare, chronic cholestatic liver diseases. Cholestasis-associated pruritus is one of the major clinical symptoms in PSC and PBC and is reported by up to 70% of patients at some point of their disease. Cholestasis-associated pruritus is also present in other causes of chronic biliary obstruction, and in all cases, may have a detrimental effect on health-related quality of life.

Pruritus in cholestasis is characterised by a diurnal rhythm, with the highest itch intensity early at night and often at the limbs (including palms of hands and soles of the feet, though patients may also experience generalised pruritus).

It is recommended that patients presenting to secondary/tertiary care with worsening itch initially undergo imaging (by MRCP) to exclude biliary obstruction and then be reviewed in a specialist benign multidisciplinary team meeting prior to starting drug therapy.

4. General management advice

Patients will be seen in clinic (secondary/tertiary care) and ongoing advice will be provided regarding non-pharmacological measures to help with pruritus. These can be useful in managing mild pruritus and in addition to pharmacological therapy in those with moderate to severe pruritus:

- Cold baths/showers
- Hydrating the skin immediately after a bath/shower
- Using unscented moisturisers
- Wearing loose clothes made of natural fibres
- Maintaining a lower room temperature
- Avoiding hot environments and dry conditions

Management of pruritus is usually monitored using a Visual Analogue Scale (VAS) where patients are asked to grade their current itch on a scale of 0 to 10 (0 being no itch and 10 being worst imaginable itch). This tool is used in outpatient clinics and is easy-to-use in the community to monitor patients on treatment for pruritus.

5. Roles and responsibilities

5.1 Criteria

Drug treatments used for management of cholestatic pruritus will be prescribed for the treatment of adults with a confirmed diagnosis of PBC or PSC who are experiencing pruritus, as per the formulary approval via the NCL Joint Formulary Committee in March 2022. Initiation of the treatment and dose titration will take place under the care of hepatology until the patient has been stabilised on a dose, with time allowed for common adverse events and side effects to have occurred before referral for continuation of prescribing and monitoring to the GP.

5.1a Transfer of care to primary care

A minimum period of one to three months stabilisation is required before transfer of prescribing responsibility to the GP. The Hospital team will ensure the patient will have at least one months' supply of medication from the time that prescribing is transferred to primary care.

5.2 Responsibilities

Specialist

1. Before initiating treatment, perform all necessary assessments and tests including itch severity assessment(VAS) , compatibility with concomitant medication(s)/disease stage, baseline bloods and radiological examination where relevant to exclude other causes of pruritus.
2. Support shared decision making with the patient (in line with NICE guideline NG197). This includes explaining aims of treatment, discussing the benefits and side effects of each option, exploring the patients aims & beliefs associated with treatment and addressing any questions/concerns.
3. Provide the patient with the relevant medication(s) Patient Information Leaflet, explain it and ensure that the patient understands the reason for the treatment, and dosing regimen. Inform the patient that treatment is off-label, where applicable.
4. Initiate treatment, optimise (stabilise) and prescribe in accordance with locally agreed pathway until the GP takes on prescribing responsibility (timescale will be dependent on individual dose titration but typically after 1-3 months).
5. Discuss the arrangement for continued prescribing with the patient.
6. Send a letter to the GP requesting continued prescribing responsibility. The letter should contain the medication, dose and frequency (as decided by the hospital team), results of baseline tests, monitoring tests & frequency (if different from this guidance), and contact details for the specialist team.
7. Patients will be seen in clinic and monitored regularly at routine clinic appointments.
8. Send a letter to the GP after each clinic attendance ensuring current dose, and frequency of monitoring are stated where relevant (including communication of any dose changes)
9. Inform GP of test results, actions to take in case of abnormal results, and advise the GP on when to adjust the dose, stop treatment, or consult with specialist
10. Evaluate adverse effects reported by GP or patient
11. Report adverse events to the MHRA (via yellow card scheme) and GP
12. Inform GP of patients who do not attend clinic appointments
13. GPs are able to obtain advice and support from the specialist.

General Practitioner

If there are concerns about the treatment there should be liaison with the specialist to resolve concerns.

1. Monitor patient's overall health and well-being and offer follow up and monitoring of itch and any relevant blood tests (see clinical monitoring section for relevant drug section below). General management advice (see

section 4) can be reinforced for patient education. Blood results are requested to be emailed to rf-tr.autoimmune-pbcmdt@nhs.net

2. Prescribe the drug treatment as described by the specialist team. Clear dosing instructions should be stated in the prescription as indicated in the hospital letter from the specialist.
3. Ensure that the patient understands the dosing on each interaction with the GP.
4. Take the opportunity at each interaction to ensure the patient understands that he/she must report the warning symptoms as listed under "adverse effects" for the respective medication below
5. Ensure compatibility with any new concomitant medication that may be initiated in primary care and liaise with specialist if any concern(s).
6. Monitor results at recommended frequencies as described under "monitoring" for each respective medication below and inform the Specialist if abnormal. *Contact details of the relevant specialist(s) are available at the end of this document.*
7. Adjust the dose as advised by the specialist (where applicable) and counsel patient on any dose changes
8. Seek advice (over the phone or by requesting a review in the clinic) whenever there are concerns or questions about the patient's ongoing treatment with medication for cholestatic pruritus
9. Report any adverse events and non-compliance to the specialist, where appropriate
10. Stop treatment on advice of specialist or immediately if urgent need arises (see "adverse effects" under each respective medication below for more details where urgent treatment cessation may be desirable)
11. Help in monitoring the progression of disease (including but not limited to worsening pruritus and liver decompensation events as per usual practice) and inform the specialist team of any changes to medication
12. Report adverse events to the specialist and MHRA (See 'Adverse effects' section of document)
13. All requests for repeat prescriptions should be reviewed individually prior to issuing

Patient responsibilities

The patient will be informed of their responsibilities when initiating treatment for the management of pruritus and supported in shared decision making. This will be reiterated throughout treatment across primary, secondary and tertiary care to ensure adherence and better patient outcomes.

1. Attend all hospital and GP appointments. If the patient does not attend their appointment they may be discharged from the service.
2. Take medicines as agreed
3. Report to the specialist or GP if he/she does not have a clear understanding of the treatment
4. Inform specialist or GP of any other medication being taken, including over-the-counter products
5. Report any adverse effects or warning symptoms to GP or specialist
6. Inform hospital and GP of any changes in address or telephone numbers

Integrated Care Board

1. To provide feedback on any prescribing-related concerns/issues to Trusts directly or via the NCL Shared Care Group.
2. To support GPs in the use and implementation of this guideline in primary care.
3. To support Trusts in resolving issues that may arise during transfer of care to primary care.

SUPPORTING INFORMATION

For further details refer to the manufacturer's Summary of Product Characteristics (SPC) www.medicines.org.uk or current BNF www.bnf.org/bnf

6. Treatment pathway in patients with cholestatic pruritus

This section outlines the treatment pathway of patients with cholestatic pruritus which is:

- Colestyramine (1st line) (or colesevelam* as alternative 1st line if colestyramine not tolerated/contra-indicated)
- Bezafibrate* (2nd line)
- Naltrexone* (3rd line)
- Sertraline* (4th line)
- Rifampicin* (5th line)

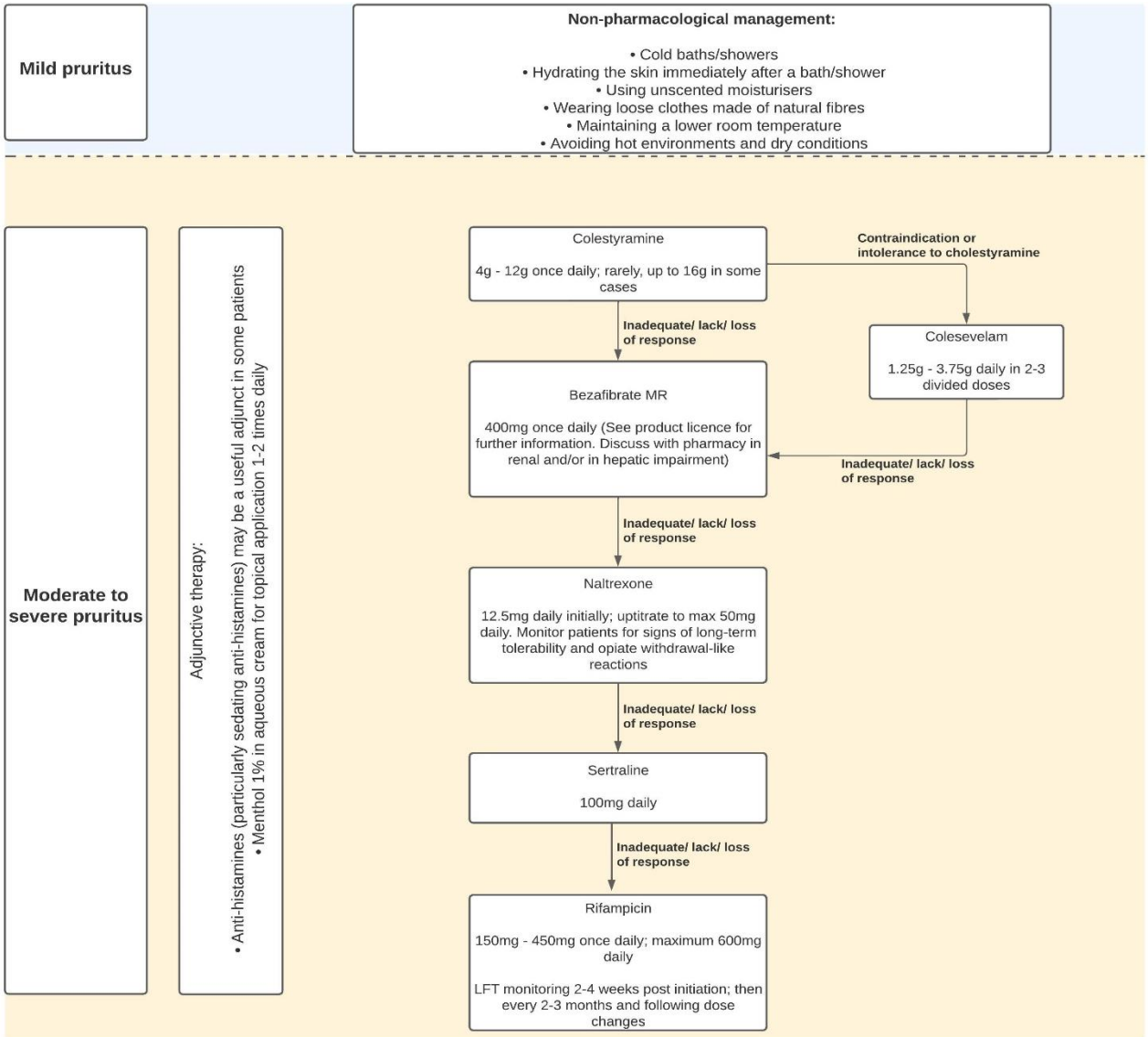
**off-label indication.*

See flow chart below illustrating treatment options.

Note, that the following therapies can be useful **adjuncts** in management of pruritus:

- Anti-histamines (particularly sedating anti-histamines such as chlorphenamine)
- Menthol 1% in aqueous cream for topical application 1-2 times daily (GPs may be asked to prescribe this if necessary)

Figure 1 - Treatment pathway for cholestatic pruritus in North Central London



6.1 Colestyramine

Colestyramine	
Dose and administration	4g - 12g once daily (rarely, up to 16g in some cases) Colestyramine should not be taken in its dry form; it should be administered mixed with water or a suitable liquid, such as fruit juice, and stirred to a uniform consistency. Colestyramine may also be mixed with skimmed milk, thin soups, pulpy fruits with high moisture content, e.g. apple sauce etc.
Renal impairment	No dose adjustment required
Hepatic impairment	No dose adjustment required
Pregnancy and breast feeding	The safety of colestyramine in pregnancy and lactation has not been established and the possibility of interference with absorption of fat-soluble vitamins should be considered.
Contraindications	Hypersensitivity to the active substance or to any of the excipients. In patients with complete biliary obstruction, since Colestyramine cannot be effective where bile is not secreted into the intestine
Special warnings and Precautions for use	Colestyramine interferes with the absorption of fat-soluble vitamins during prolonged high dose administration. Supplementation with vitamins A, D, K and folic acid may be required. Colestyramine may be associated with increased bleeding risk due to Vitamin K deficiency. This will usually respond promptly to parenteral Vitamin K administration. Recurrences can be prevented by Vitamin K supplementation. There is a possibility that prolonged use of colestyramine resin in high doses may produce hyperchloremic acidosis, since it is the chloride form of an anion exchange resin. This is especially true in younger and smaller patients where the relative dosage may be higher. 'Questran Light' contains aspartame (a source of phenylalanine) and can be harmful to individuals with phenylketonuria.
Discontinuing treatment	Can be discontinued if not tolerated/no longer indicated

Adverse effects ***- list not exhaustive (see SPC for further information)***

Adverse effect	**Frequency**	**Suggested management by GP**
Constipation	Very common	Most instances of constipation are mild, transient and controlled with conventional therapy. This may require a temporary decrease in dosage or discontinuation of therapy.
Bleeding tendencies due to hypoprothrombinaemia (Vitamin K deficiency)	Uncommon	Administer parenteral vitamin K, stop colestyramine and refer to specialist for review.
Vitamin D deficiency	Uncommon	Manage as per local practice
Night blindness (Vitamin A deficiency)	Rare	Refer to specialist for review
Intestinal obstruction	Rare	Refer for urgent medical assessment

Monitoring	No specific monitoring is required for colestyramine
Drug interactions	Patients should take **other drugs at least one hour before or 4-6 hours after Colestyramine to minimise possible interference with their absorption.** Colestyramine may delay or reduce the absorption of certain drugs (such as digitalis, tetracycline, chlorothiazide, warfarin and thyroxine). The response to concomitant medication should be closely monitored and appropriate adjustments made if necessary. Colestyramine may interfere with the pharmacokinetics of drugs that undergo enterohepatic recirculation.
Important links	SPC (see references section) BNF monograph

6.2 Colesevelam

Colesevelam	
Dose and administration	1.25g - 3.75g daily in 2-3 divided doses. Colesevelam tablets should be taken orally with a meal and liquid. The tablets should be swallowed whole and not broken, crushed or chewed.
Renal impairment	No dose adjustment required
Hepatic impairment	No dose adjustment required
Pregnancy and breast feeding	No clinical data are available on the use of colesevelam in pregnancy and safety has not been established in breastfeeding women. Caution should be exercised when prescribing to pregnant and breastfeeding women.
Contraindications	Hypersensitivity to the active substance or to any of the excipients. Bowel or biliary obstruction.
Special warnings and Precautions for use	Secondary causes of hypercholesterolaemia should be diagnosed and properly treated, if considered, prior to initiating colesevelam Caution should be exercised if triglyceride levels > 3.4 mmol/l due to the triglyceride increasing effect with colesevelam (these patients were excluded from clinical studies) Caution should be exercised in dysphagia, swallowing disorders, severe gastrointestinal motility disorders, inflammatory bowel disease, liver failure or major gastrointestinal tract surgery (safety and efficacy of colesevelam not established in these patients) Constipation can be induced or worsened with Colesevelam. Special consideration is advised in patients with coronary heart disease and angina pectoris.
Discontinuing treatment	Can be discontinued if not tolerated/no longer indicated

Adverse effects- ***list not exhaustive (see SPC for further information)***

Adverse effect	Frequency	Suggested management by GP
Flatulence, Constipation	Very common	Manage as per local practice
Headache	Common	
Vomiting, diarrhoea, dyspepsia, abdominal pain, abnormal stools, nausea, abdominal distension	Common	
Serum triglycerides increased	Common	Assess cardiovascular risk and manage as per local practice.
Serum transaminases increased	Uncommon	Transaminases will be monitored by specialist in secondary care under usual monitoring. Refer to specialist in case of transaminases derangement.
Pancreatitis	Very rare	Stop Colesevelam and refer for urgent medical assessment.

Monitoring	No specific monitoring is required for colesevelam
Drug interactions	In general, Colesevelam may affect the bioavailability of other medicinal products. Therefore, when a drug interaction cannot be excluded with a concomitant medicinal product for which minor variations in the therapeutic level would be clinically important, colesevelam should be administered **at least four hours before or at least four hours after the concomitant medication** to minimise the risk of reduced absorption of the concomitant medication. For concomitant medications, which require administration via divided doses, it should be noted that the required dose of colesevelam can be taken once a day. Examples of drug groups where this interaction may be relevant (list not exhaustive) include: levothyroxine, oral contraceptives, anticoagulants, ciclosporin.
Important links	SPC (see references section) BNF monograph

6.3 Bezafibrate

Bezafibrate *modified-release formulation*	
Dose and administration	The dose for bezafibrate MR is 400mg once a day taken after a meal either in the morning or at night. For patients with gastric sensitivity, the dose may be gradually increased over 5-7 days to the maintenance level of 400mg OD.
Renal impairment	See contraindications section. Note, patients with renal impairment (CrCl<60ml/min) may be treated with immediate release tablets using an appropriately reduced daily dose.
Hepatic impairment	See contraindications section. Note, in some cases, Bezafibrate may be used in hepatic impairment or in jaundiced obstructed patients under the supervision of a hepatologist only.
Pregnancy and breast feeding	Not recommended during pregnancy and in women of childbearing potential not using contraception. A clinical assessment must be made for use in breastfeeding.
Contraindications	• Patients with nephrotic syndrome and severe renal impairment (serum creatinine >135micromol/l or CrCl<60ml/min) – *see renal impairment section above* • Significant hepatic disease (other than fatty infiltration of the liver associated with raised triglyceride values) – *see hepatic impairment section above* • Gall bladder disease with or without cholelithiasis– *see hepatic impairment section above* • Patients requiring dialysis • Concomitant use of HMG CoA reductase inhibitors (statins) in patients with predisposing factors for myopathy (see cautions below) • Hypersensitivity to bezafibrate or any component of the product or to other fibrates • Known photoallergic or phototoxic reactions to fibrates
Special warnings and Precautions for use	• Bezafibrate may cause myopathy, symptoms of which include muscle weakness or pain accompanied by a considerable increase in creatinine kinase. In isolated cases, rhabdomyolysis may occur. The risk of rhabdomyolysis may be increased when higher than recommended doses of bezafibrate are used, most frequently in the presence of impaired renal function and in patients with predisposing factors for myopathy (including renal impairment [CrCl<60ml/min], age>65years, personal or familiar history of hereditary muscular disorders and previous history of muscular toxicity with a fibrate of other lipid lowering drugs, hypothyroidism, severe infection, trauma, surgery, disturbances of hormone or electrolyte imbalance and a high alcohol intake) • Bezafibrate should be used with caution in combination with HMG CoA reductase inhibitors as this combination is shown to increase the incidence and severity of myopathy. Patients should be informed of symptoms and monitored for signs of myopathy and increased creatinine kinase activity. This combination should be discontinued if signs of myopathy develop. Combination therapy should not be used in patients with predisposing factors for myopathy (as above) • Bezafibrate alters the composition of bile. There have been isolated reports of the development of gallstones. • The prescribing of bezafibrate in patients taking oestrogens or oestrogen containing contraceptives must be critically considered on an individual basis.
Discontinuing treatment	Can be discontinued if not tolerated/no longer indicated. Decisions to discontinue Bezafibrate will be made in the outpatient clinic.

Adverse effects - *list not exhaustive (see SPC for further information)*

Adverse effect	Frequency	Suggested management by GP
Decreased appetite	Common	Monitor and inform specialist if troublesome.
Gastrointestinal disorders	Common	Monitor and inform specialist if troublesome.
Acute renal failure	Uncommon	Discontinue Bezafibrate and inform specialist.
Pancreatitis	Rare	Discontinue Bezafibrate, inform specialist and refer for relevant management
Rhabdomyolysis	Very rare	Discontinue Bezafibrate, refer for relevant management and inform specialist
Cholelithiasis	Very rare	Refer for further investigation as appropriate diagnostic procedures should be performed if cholelithic symptoms and signs occur

Effects on ability to drive and operate machinery: Bezafibrate MR 400mg Tablets have been shown to cause dizziness and can have a minor to moderate effect on the ability to drive or operate machinery. Patients should not drive or use machines if affected.

<table>
<tr><td>Monitoring</td><td>
<table>
<tr><th>Monitoring</th><th>Frequency</th><th>Action if out of range</th></tr>
<tr><td>Full Blood Count (FBC)</td><td rowspan="6">6 monthly once stable. In case of dose change, recheck FBC, LFT, U+E, TFT, CK, Triglycerides 1 month post dose change and then 3 monthly, followed by 6 monthly once stable.</td><td>Investigate common causes and inform specialist.</td></tr>
<tr><td>Liver Function Tests (LFT’s)</td><td>Inform specialist. Particularly if progression of liver disease from baseline (e.g. rise in ALP and/or bilirubin)</td></tr>
<tr><td>Urea & Electrolytes (U&E’s)</td><td>Investigate as per local practice. Note, Bezafibrate is contra-indicated in serum creatinine >135micromol/l or CrCl<60ml/min</td></tr>
<tr><td>Thyroid Function Test (TFT)</td><td>Manage as per local practice.</td></tr>
<tr><td>Creatine Kinase (CK)</td><td>In the case of raised CK accompanied by signs of rhabdomyolysis, stop Bezafibrate and refer to the specialist.</td></tr>
<tr><td>Triglycerides</td><td>Manage as per local practice.</td></tr>
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<tr><td>Drug interactions</td><td>

Coumarins – action may be potentiated. Reduce anticoagulant dose by up to 50%, monitor coagulation and readjust as necessary
Antidiabetic medication (including Insulin) – action may be potentiated. Monitor glucose control closely for the first 3 months
Ion-exchange resins – impairs absorption of bezafibrate, ensure two hour gap between resin and bezafibrate
MAO inhibitors – do not co-administer
Immunosuppressants –In isolated cases, a pronounced though reversible impairment of renal function (accompanied by a corresponding increase in serum creatinine level) has been reported in organ transplant patients receiving immuno-suppressant therapy and concomitant bezafibrate. Therefore, it is advised to monitor renal function closely
HMG CoA reductase inhibitors (including atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin) - increased risk of myopathy (if used concomitantly, see individual SPC’s for maximum daily dose advice for chosen statin)
Colchicine - increased risk of myopathy

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<tr><td>Important links</td><td>SPC (see references section)
BNF monograph</td></tr>
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6.4 Naltrexone

Naltrexone	
Dose and administration	Initial dose of 12.5mg daily which can be up-titrated to a maximum dose of 50mg daily. The dose should be titrated slowly to avoid withdrawal symptoms.
Renal impairment	Cautioned in renal impairment as naltrexone is excreted predominantly in the urine. Patient suitability will be assessed on an individual basis.
Hepatic impairment	Cautioned in hepatic impairment as naltrexone is extensively metabolised in the liver. Patient suitability will be assessed on an individual basis under the supervision of a hepatologist.
Pregnancy and breast feeding	There are no clinical data on Naltrexone use in pregnancy. Naltrexone should only be given to pregnancy women when, in the judgement of the attending physician, the potential benefits outweigh the possible risks. Breastfeeding is not recommended during Naltrexone treatment.
Contraindications	• Hypersensitivity to Naltrexone hydrochloride or to any of the product excipients • Acute hepatitis or liver failure • Severe renal failure • in patients currently dependent on opioids (risk of acute withdrawal syndrome) • in any patient who has a positive screen for opioids or who has failed the naloxone provocation test • for use in conjunction with an opioid – containing medication • in combination with methadone (see Drug Interactions below)
Special warnings and Precautions for use	• Impaired hepatic or renal function. • A withdrawal syndrome may be precipitated in opioid dependent patients; signs and symptoms may develop within 5 minutes and last up to 48 hours. Treatment should be symptomatic (may include opioid administration) • In an emergency situation in which the administration of opioid analgesics is required in patients receiving Naltrexone, a higher than usual dose of opioid analgesics may be administered to have the same therapeutic effect. The resulting respiratory depression may be deeper and more prolonged and non-receptor mediated effects may also appear (e.g. swelling of the face, pruritus, generalized erythema, diaphoresis, and other dermal and mucosal symptoms presumably due to histamine liberation). In these circumstances, the patient must be carefully monitored by trained personnel in a hospital setting. • Painful conditions should be treated with non-opioid analgesia only whilst patients are taking Naltrexone • Patients should be warned that attempts to overcome the blockade by administering large doses of opioids may result in an acute opioid intoxication after the end of the Naltrexone hydrochloride effect which may be possibly life threatening. High dose opioid intake, concomitant with Naltrexone hydrochloride treatment, can lead to life-threatening opioid poisoning from respiratory and circulatory impairment. • Patients must be warned against the concomitant use of opioids (e.g. opioids in cough medication, opioids in symptomatic medication for the treatment of common colds, or opioids contained in anti-diarrhoeal agents, etc.) during Naltrexone hydrochloride treatment (see Naltrexone contraindications section above) • Naltrexone hydrochloride treatment must begin only when the opioid has been discontinued for a sufficiently long period (about 5 to 7 days for heroin and at least 10 days for methadone) • Patients might be more sensitive to opioid containing medicines after treatment with Naltrexone hydrochloride. • Lactose: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Discontinuing treatment	Can be discontinued if not tolerated/no longer indicated.

Adverse effects - *list not exhaustive (see SPC for further information)*

Adverse effect	Frequency	Suggested management by GP
Anxiety, insomnia, headache, asthenia	Very common	Monitor adverse events as per local practice and inform specialist if troublesome.
Abdominal pain, nausea and/or vomiting		
Arthralgia and myalgia		
Irritability, affective disorders	Common	Monitor adverse events as per local practice and inform specialist if troublesome.
Dizziness		
Increased eye lacrimation		
Tachycardia, palpitations, electrocardiogram change		
Chest pain		
Diarrhoea, constipation		
Decreased appetite		
Thirst, energy increased, chills, hyperhidrosis		
Hallucination, confusional state, depression, paranoia, disorientation, nightmare, agitation, libido disorder, abnormal dreams	Uncommon	Monitor adverse events as per local practice and inform specialist if troublesome.
Suicidal ideation, attempted suicide	Rare	Discontinue Naltrexone and refer to specialist
Rhabdomyolysis	Very rare	Discontinue Naltrexone, refer for relevant management and inform specialist

Effects on ability to drive and operate machinery: Naltrexone hydrochloride may impair the mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery.

Monitoring

Test	Frequency	Action if out of range
Liver Function Tests (LFT's)	At baseline, then 6 monthly once stable. *In case of dose change, recheck LFT's and U&E's 1 month post dose change, then 3 monthly followed by 6 monthly once stable*	Inform specialist for review in outpatient setting. Note, naltrexone should be discontinued if the patient develops acute hepatitis/liver failure and referred for urgent management
Urea & Electrolytes (U&E's)		Inform specialist for review in outpatient setting. Note, naltrexone should be discontinued if the patient develops severe renal failure and referred for urgent management.

Drug interactions

Concomitant administration of Naltrexone hydrochloride with an opioid-containing medication should be avoided. Association to be taken into account: barbiturates; benzodiazepines, anxiolytics others than benzodiazepines (i.e. meprobamate), hypnotics, sedative antidepressants (amitriptyline, doxepin, mianserin, trimipramine), sedative antihistaminics H1, neuroleptics (droperidol).

It is not recommended to take Naltrexone together with Central antihypertensives (such as alpha-methyldopa).

Important links

SPC (see references section)
BNF monograph

6.5 Sertraline

Sertraline	
Dose and administration	100mg daily once daily, either in the morning or evening (with or without food)
Renal impairment	No dose adjustment required
Hepatic impairment	Caution – sertraline should not be initiated for cholestatic pruritus without hepatology input. Sertraline should not be used in severe hepatic impairment as no clinical data are available.
Pregnancy and breast feeding	Not recommended in pregnancy unless benefit of the treatment is expected to outweigh the potential risk. During breastfeeding, small quantities of sertraline and its metabolite are excreted in milk. To date, no adverse effects on the health of infants nursed by mothers using sertraline have been reported, but a risk cannot be excluded. Use in nursing mothers is not recommended unless, in the judgment of the physician, the benefit outweighs the risk.
Contraindications	• Hypersensitivity to the active substance or any of the product excipients • Concomitant treatment with irreversible monoamine oxidase inhibitors (MAOIs) due to the risk of serotonin syndrome. Sertraline must not be initiated for at least 14 days after discontinuation of treatment with an irreversible MAOI. Sertraline must be discontinued for at least 7 days before starting treatment with an irreversible MAOI • Concomitant intake of pimozide
Special warnings and Precautions for use	• **Life-threatening Serotonin syndrome or Neuroleptic Malignant Syndrome** has been reported with Selective Serotonin Reuptake Inhibitors (SSRIs), including sertraline. The risk is increased when SSRIs are used with other serotonergic drugs, drugs that impair metabolism of serotonin, antipsychotics and other dopamine antagonists and with opiate drugs. • **Switching from SSRIs, antidepressants or anti-obsessional drugs**: care should be exercised when switching, particularly from long-acting agents such as fluoxetine • **QTc Prolongation/Torsade de Pointes:** caution in patients with additional risk factors for QTc prolongation such as cardiac disease, hypokalaemia or hypomagnesemia, familial history of QTc prolongation, bradycardia and concomitant use of medications with prolong QTc interval • **History of hypomania/mania:** Discontinue Sertraline in any patient entering a manic phase. • **Schizophrenia:** psychotic symptoms might become aggravated • **Seizures:** avoid sertraline in unstable epilepsy and those with controlled epilepsy should be carefully monitored. Sertraline should be discontinued in any patient who develops seizures • **Suicide/suicidal thoughts/suicide attempts:** Patients (and caregivers) should counselled to monitor for any clinical worsening, suicidal behaviour thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present. • **Sexual dysfunction:** There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs. • **Abnormal bleeding/haemorrhage:** Bleeding abnormalities (including cutaneous bleeding) and other haemorrhagic events (sometimes fatal) such as gastrointestinal or gynaecological bleeding have been reported. Caution is advised, particularly in concomitant use with drugs known to affect platelet function as well as in patients with a history of bleeding disorders. • **Akathisia/psychomotor restlessness symptoms** has been associated with sertraline (most likely to occur within first few weeks). Increasing the dose may be detrimental in these symptoms • **Angle-Closure glaucoma:** sertraline may have an effect on pupil size resulting in mydriasis.
Discontinuing treatment	Abrupt discontinuation should be avoided. When stopping treatment, the dose should be gradually reduced over at least one to two weeks in order to reduce the risk of withdrawal symptoms (such as dizziness, sensory disturbances, sleep disturbances, anxiety, nausea, vomiting, tremor headache). These tend to occur in first few days of discontinuing treatment, are generally mild to moderate and self-limiting (usually resolve within 2 weeks). If intolerable symptoms occur, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose at a more gradual rate according to the patient's needs.

Adverse effects - ***list not exhaustive (see SPC for further information)***

Adverse effect	Frequency	Suggested management by GP
Insomnia, Dizziness, headache, somnolence, fatigue	Very common	Monitor and manage as per local practice. Inform specialist if adverse effects become troublesome.
Nausea, diarrhoea, dry mouth		
Ejaculation failure		
Upper respiratory tract infection, pharyngitis, rhinitis	Common	Monitor and manage as per local practice. Inform specialist if adverse effects become troublesome.
Anxiety, depression, agitation, libido decreased, nervousness, depersonalisation, nightmare, bruxism		
Tremor, movement disorders (including extrapyramidal symptoms), paraesthesia, hypertonia, attention disturbance, dysgeusia		
Visual disturbance		
Tinnitus		
Palpitations, Malaise, chest pain, asthenia, pyrexia		
Hot flush		
Yawning		
Dyspepsia, constipation, abdominal pain, vomiting, flatulence, decreased/increased appetite, weight increased		
Hyperhidrosis, rash		
Back pain, arthralgia, myalgia		
Irregular menstruation, erectile dysfunction		
ALT increased, AST increased	Uncommon	Refer to specialist for further investigation
Diverticulitis	Rare	Refer for relevant management, consider stopping Sertraline and inform specialist.
Leukopenia, thrombocytopenia, leukopenia		
Interstitial lung disease		
Pancreatitis		
Hyponatraemia		
Serious liver events (including hepatitis, jaundice and hepatic failure)		
Severe cutaneous adverse reactions e.g. Stevens-Johnson syndrome		
Rhabdomyolysis		

Effects on ability to drive and operate machinery: Studies have shown that sertraline has no effect on psychomotor performance. However, as psychotropic drugs may impair the mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, the patient should be cautioned accordingly.

Monitoring	No specific biochemical monitoring is required. GP's should review their patients as per their normal practice.
Drug interactions	• **Lithium:** coadministration may result in an increase in tremor. • **Phenytoin:** dose adjustment may be required upon sertraline initiation (monitor plasma phenytoin levels) • **Triptans:** rare patient reports of weakness, hyperreflexia, incoordination, confusion, anxiety and agitation following use of sertraline and sumatriptan. Serotonergic syndrome may occur with other triptans also. • **Warfarin:** coadministration may increase prothrombin time which may, in rare cases, unbalance the INR value. • **Cimetidine:** coadministration can substantially decrease sertraline clearance (clinical significance unknown) • **CYP 2D6 substrates:** sertraline may increase levels of drugs which are substrates of CYP 2D6 and this may be clinically relevant with narrow therapeutic index, especially at higher sertraline dose levels. • **Potent and moderate CYP3A4 inhibitors:** may increase levels of sertraline (combination not recommended). • **Strong CYP2C19 inhibitors:** potential for increase in sertraline levels. • **Grapefruit juice**: coadministration not recommended as can lead to increased sertraline levels • **In patients with diabetes:** Insulin and/or oral hypoglycaemic dosage may need to be adjusted.
Important links	SPC (see references section) BNF monograph

6.6 Rifampicin

Rifampicin	
Dose and administration	150mg - 450mg once daily; maximum 600mg daily. Rifampicin should preferably be taken on an empty stomach or at least 30 minutes before a meal or 2 hours after a meal to ensure rapid and complete absorption.
Renal impairment	No dose adjustment required in doses of up to 600mg/day.
Hepatic impairment	Use cautioned – see clinical monitoring section.
Pregnancy and breast feeding	Rifampicin can be used in pregnant women or in women of child bearing potential only if the potential benefit justifies the potential risk to the foetus. Infants should not be breast fed by a patient receiving rifampicin unless in the physician's judgement the potential benefit to the patient outweighs the potential risk to the infant.
Contraindications	• In the presence of jaundice • in patients who are hypersensitive to the active substance, rifampicin or any of the excipients in the product. • Concurrent use with the combination of saquinavir/ ritonavir.
Special warnings and Precautions for use	• Baseline liver function tests, serum creatinine and full blood count should be taken. • Patients with impaired liver function should only be given rifampicin in cases of necessity, and then with caution and under close supervision under Hepatology when used for itch • Rifampicin should also be withdrawn if clinically significant changes in hepatic function occur. If rifampicin is re-introduced after liver function has returned to normal, liver function should be monitored daily. • Rifampicin has enzyme induction properties that can enhance the metabolism of endogenous substrates including adrenal hormones, thyroid hormones and vitamin D. Isolated reports have associated porphyria exacerbation with rifampicin administration. • At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. • Rifampicin capsules may produce a discoloration (yellow, orange, red, brown) of the teeth, urine, sweat, sputum and tears, and the patient should be forewarned of this. Soft contact lenses have been permanently stained. • It is important to note that early manifestations of hypersensitivity such as fever, lymphadenopathy or biological abnormalities (including eosinophilia, liver abnormalities) may be present even though rash is not evident. If such signs or symptoms are present, the patient should be advised to consult immediately their physician. If signs and symptoms suggestive of these reactions appear, Rifampicin capsules should be withdrawn immediately and an alternative treatment considered (as appropriate). Most of these reactions occurred within 2 days to 2 months after treatment initiation; the time to onset can vary depending on the conditions.
Discontinuing treatment	Can be discontinued if not tolerated/no longer indicated.

Adverse effects - *list not exhaustive (see SPC for further information)*

Adverse effect	**Frequency**	**Suggested management by GP**
Pyrexia, chills	Very common	Manage as per local practice
Blood bilirubin, AST and ALT increased	Common	See clinical monitoring section below
Thrombocytopenia with or without purpura		Monitor. Note, this is reversible if drug is discontinued as soon as purpura occurs
Headache, dizziness		
Nausea, vomiting		Manage as per local practice
Leukopenia	Uncommon	Refer to specialist for review

Discoloration (yellow, orange, red, brown) of the teeth (may be permanent), urine, sweat, sputum and tears. Soft contact lenses have been permanently stained	Unknown	Monitor as per local practice. Note, patients should be counselled on the potential for these side effects prior to initiation
Pseudomembranous colitis, Influenza		Inform specialist and discontinue Rifampicin.
Disseminated intravascular coagulation, eosinophilia, agranulocytosis, haemolytic anaemia, Vitamin K dependent coagulation disorders		See clinical monitoring section. Inform specialist for review and discontinue Rifampicin. Supplemental vitamin K administration should be considered when appropriate (vitamin K deficiency, hypoprothrombinaemia).
Erythema multiforme including Stevens-Johnson syndrome, Toxic epidermal necrolysis, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome		Discontinue Rifampicin and refer urgently for appropriate management
Acute kidney injury (usually due to renal tubular necrosis or tubulointerstitial nephritis)		Discontinue Rifampicin, refer for relevant management and inform specialist

Monitoring

Test	Frequency	Action if out of range
Liver Function Tests (LFT's)	Once stable, every 2-3 months. *In case of dose change, check LFT's after 2-4 weeks, then every 2-3 months if stable.*	Inform specialist for review in outpatient setting. Note, Rifampicin should be discontinued if clinically significant alteration in hepatic function occurs and the patient referred for urgent management
Urea & Electrolytes (U&E's)		Inform specialist for review in outpatient setting. Note, Rifampicin should be discontinued if the patient develops acute kidney injury.
Full blood count (including clotting screen)		Inform specialist for review in outpatient setting and consideration of supplemental vitamin K, if appropriate

Drug interactions

Rifampicin is a well characterized and potent inducer of drug metabolizing enzymes and transporters. Therefore, Rifampicin may accelerate the metabolism and reduce the activity of certain co-administered drugs, and has the potential to perpetuate clinically important drug-drug interactions against many drugs and across many drug classes. To maintain optimum therapeutic blood levels, dosages of drugs may require adjustment when starting or stopping concomitantly administered Rifampicin.

For a full list of these interactions, please refer to SPC/BNF for information on interactions with Rifampicin and how to manage these interactions.

Interactions may include:

- **Oral contraceptives:** patients on oral contraceptives should be advised to use alternative, non-hormonal methods of birth control during rifampicin therapy as rifampicin reduces the systemic exposure of oral contraceptives.
- **Antacids:** concomitant administration may reduce absorption of rifampicin. Daily doses of rifampicin should be given at least 1 hour before the ingestion of antacids.
- **Halothane:** concomitant use should be avoided due to increased potential for hepatotoxicity
- **Other antibiotics causing vitamin K dependent coagulopathy such as cefazolin (or other cephalosporins with N-methyl-thiotetrazole side chain)** should be avoided as it may lead to severe coagulation disorders, which may result in fatal outcome (especially in high doses)

Important links

SPC (see references section)
BNF monograph

7. Contact Details

Royal Free Hospital – Liver Unit					
Switchboard number:				020 7794 0500	
Hepatology Consultants					
Prof R Jalan	Ext 36167	Dr R Westbrook	Ext 38097	**Specialist Pharmacists:** Bleep 1353 /1961	
Prof K Moore	Ext 34357	Prof M Pinzani	Ext 32851		
Dr R Mookerjee	Ext 36167	Dr E Tsochatzis	Ext 33575	**Secretary email address:**	
		Dr D MacDonald	Ext 35056	rf-tr.hepatologyadmin@nhs.net	
Dr D Patch	Ext 38097	Dr A Marshall	Ext 38325		
Dr D Thorburn	Ext 31142	Dr A O'Brien	Ext 36167		
Dr L China	Ext 38097	Dr J Ryan	Ext 36167		
Dr J Potts	Ext 38325				
CNS Hepatology:					
rf-tr.autoimmune-pbcmdt@nhs.net		Hepatology Registrar		Pharmacy Medicines Advice service: 0207 830 2983 (*Mon-Fri, 11am – 5pm)*	
Tel: 07773582584		on-call bleep 2530		Email: rf.medicinesadvice@nhs.net	

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