Mid and South Essex Health and Care Partnership

NHS

Mid and South Essex Medicines Optimisation Committee (MSEMOC)

FIBRATES (BEZAFIBRATE AND FENOFIBRATE) FOR THE MANAGEMENT OF ADULTS WITH PRIMARY BILIARY CHOLANGITIS (PBC)

RED: RECOMMENDED FOR RESTRICTED USE in Secondary Care by Gastroenterology Specialists

Name: Generic	What it is	'Off label' indication	Decision status	NICE/SMC guidance
Bezafibrate & Fenofibrate	**Fibric acid derivate**	**As add on or second line therapy in adults for the management of Primary Biliary Cholangitis**	**Final**	**NICE – no guidance SMC- no guidance**

MSEMOC recommendation:

Bezafibrate and fenofibrate are RECOMMENDED FOR RESTRICTED USE, either as ADD ON or SECOND LINE THERAPY for the MANAGEMENT OF PRIMARY BILIARY CHOLANGITIS in ADULTS:

- **For initiation and continuation in secondary care by gastroenterology specialists only**
- **Restricted for use as:**
  - **An add on therapy to ursodeoxycholic acid (UDCA)**
  - **A second line therapy for patients intolerant to, or not responding to, UDCA or obeticholic acid (OCA).**

Providers commissioned to provide services on behalf of Mid and South Essex CCGs are reminded that they are required to follow the local joint formulary and prescribing guidance, as detailed in the medicines management service specification of their contract

Background information:

- Fibrates therapy (bezafibrate and fenofibrate) is licensed in the UK for the management of dyslipidaemias.
- Primary biliary cholangitis (formerly known as primary biliary cirrhosis, PBC) is an autoimmune liver disease in which a cycle of immune mediated biliary epithelial cell injury, cholestasis and progressive fibrosis can culminate over time in an end-stage biliary cirrhosis
- Licensed therapies for the management of PBC include ursodeoxycholic acid (UDCA) and obeticholic acid (OCA).
- Disease management focuses on initiation of UDCA for all patients and risk stratification based on baseline and on-treatment factors, including in particular the response to treatment
- The European Association for the Study of the Liver (EASL) guidelines have included second line 'off label' fibrates as potential add on therapy options to UDCA non-responders alongside the alternative, licensed OCA.

ASSESSMENT AGAINST THE ETHICAL FRAMEWORK

Evidence of Clinical Effectiveness

Study: Corpechot, C et al., 2017. A Placebo-Controlled (BEZURSO trial) Trial of Bezafibrate in Primary Biliary Cholangitis,

The BEZURSO trial is the first and currently only available placebo-controlled trial on the efficacy and safety of a fibrate in patients with PBC.

- Objective: Review of the effects of fibrates and use as a second-line option for PBC in patient with incomplete response to or intolerance to Ursodeoxycholic acid against a placebo.
- Design: A 24-month, randomized, double-blinded, placebo-controlled study. Patients randomised 1:1.
- Patients: 100 patients with inadequate biochemical response to UDCA according to the Paris 2 criteria (ALP or AST levels > 1.5 times ULN, or elevated total bilirubin). Half the patients enrolled were at an advanced stage of the disease (Ludwig's stage III–IV) or liver-stiffness measurement (> 9.6 kPa). Patients with decompensated cirrhosis or a total bilirubin level > 3 mg/dL and those with typical features of autoimmune hepatitis at baseline were non-eligible.
- Intervention and Comparison: patient received bezafibrate or placebo, in addition to continued treatment with UDCA for 24 months. Two patients (4%) in the bezafibrate group and 6 (12%) in the placebo group withdrew from the trial.
- Primary Outcome- the percentage of patients achieving normal levels of bilirubin, ALP, aminotransferases, albumin, and prothrombin index at 24 months;31% of the patients in the bezafibrate group and 0% in the placebo group ($p < 0.001$). Normal levels of ALP observed in 67% of the patients in the bezafibrate group and in 2% in the placebo

group ($p < 0.001$); Changes in total bilirubin, ALP, GGT, and transaminases were consistent with the result of the primary endpoint.

- Other Outcomes:
  Changes in pruritus, fatigue, and non-invasive markers of liver fibrosis (including liver stiffness and Enhanced Liver Fibrosis score).
  Levels of IgM decreased by 21% in the bezafibrate group and in 2% in the placebo group, but the difference did not reach the level of significance.
  Patients with portal hypertension or high ALP levels at baseline were less likely to achieve an adequate response to bezafibrate.
  Despite improvement in biochemistries, symptoms, and surrogate markers of fibrosis in the bezafibrate group, the number of liver-related complications did not differ between treatment arms (two in each arm), thus indicating the need for longer studies to determine the effect of bezafibrate on clinical outcomes.
- Safety: Incidence rates of adverse events were similar between treatment groups.
  The percentage of patients with myalgia was higher in the bezafibrate group (20%) than in the placebo group (10%) although the difference was not significant.
  A 5% significant increase in serum creatinine level at 24 months was observed in the bezafibrate group as compared to the placebo group.
  One patient in the bezafibrate group, who had a history of diabetes and hypertension, had a decrease in the estimated glomerular filtration rate (eGFR) < 60 mL/min.
  Four patients (three in the bezafibrate group and one in the placebo group) had an increase in ALT levels > 5 times the upper limit of the normal range occurring within the first 6 months of trial. This led to a discontinuation of the active drug or placebo in three patients (two in the bezafibrate group and one in the placebo group). All cases in the bezafibrate group resolved within 3 months, either spontaneously (in one patient) or after glucocorticoid administration (two patients, in whom liver histologic features at baseline were suggestive of associated autoimmune hepatitis).
  No increase in the risk of cholelithiasis was reported in the bezafibrate group.

Study: Lens et al., 2014. Bezafibrate normalizes alkaline phosphatase in primary biliary cirrhosis patients with incomplete response to ursodeoxycholic acid (UDCA)

- Objective: a pilot study to analyse the effects of bezafibrate in patients with suboptimal response to UDCA.
- Patients and method: Thirty women (age 52.3 ± 2.3 years) treated with UDCA and abnormal alkaline phosphatase (AP) levels received bezafibrate (400 mg/d) for 1 year.
  Changes were measured every 3 months during the study period of 12 months, 3 months after discontinuation and 3 months after resuming bezafibrate.
  Two patients discontinued the treatment after few days, three at 6 and one at 9 months.
- Results: Bezafibrate treatment resulted in a significant decrease in AP as early as 3 months. Normalization or decrease of AP below 1.5 times normal levels was observed in 13 and 4 patients respectively. There was a significant decrease in c-glutamyl transferase and alanine aminotransferase, cholesterol and triglyceride levels. Bezafibrate treatment resulted in significant improvement of pruritus. A rebound in liver biochemistries and pruritus occurred upon drug discontinuation, changes which improved again after resuming bezafibrate. Response to bezafibrate was associated with lower liver stiffness and severity of cholestasis
- Conclusions: Combination treatment of bezafibrate and UDCA is associated with marked decrease or normalization of alkaline phosphatase as early as 3 months in patients with PBC. Better biochemical response was observed in patients with early disease and lower cholestasis.

Study: Levy et al., 2010. Fenofibrate for patients with primary biliary cirrhosis and an incomplete response to ursodeoxycholic acid

- Objective: This was an open label pilot study designed to provide preliminary efficacy and safety data on the use of fenofibrate in patients with PBC and incomplete response to UDCA.
- Patient and methods: Pilot study involving 20 patients with PBC and serum ALP ≥2x ULN.
  Eligibility criteria were
  (i) an established diagnosis of PBC according to published criteria,4
  (ii) age 21–75 years,
  (iii) treatment with 13–15 mg/kg/day of UDCA for at least 1 year
  and
  (iv) persistent elevation of serum ALP greater than two-fold the upper limit of normal on two separate measurements.
  Twenty patients received fenofibrate (160 mg/day) in addition to UDCA for 48 weeks.
- Primary efficacy endpoint was change in serum levels of ALP. Treatment was arbitrarily considered successful if >35% of subjects experienced at least 40% improvement in ALP, or its normalisation, without any statistically significant worsening in serum transaminases.
- Main secondary endpoints were changes in the serum IgM levels and the MRS after 1 year of treatment as compared to baseline values.
- Results: Median serum ALP decreased significantly at 48 weeks compared with baseline values [351 (214–779) U/L at baseline vs. 177 (60–384) U/L at 48 weeks, $P < 0.05$]. A rebound in ALP occurred upon drug discontinuation. Serum

aspartate aminotransferase and Immunoglobulin M also decreased significantly, while bilirubin and albumin remained unchanged. Median interleukins 1 (IL-1) decreased from 28.9 (2.7–10 000) to 11.3 (2.5–277.7) pg⁄mL (P = 0.049), and median IL-6 from 4.6 (3.2–5205) to 3.5 (3.2–73.4) pg⁄mL (P = 0.027). (Fenofibrate can inhibit factor Kappa beta and lead to decreased expression of interleukin, hence its measurement in the study). Heartburn was the most frequent adverse event, leading to discontinuation of two study subjects.

- Conclusion: Combination therapy of fenofibrate and UDCA induced significant biochemical improvement in patients with PBC and incomplete response to UDCA.

Study: Kurihara et al., 2000. Bezafibrate in the treatment of primary biliary cirrhosis: comparison with ursodeoxycholic acid (UDCA)

- Objective: A randomised comparative study of biochemical effects of bezafibrate and UDCA in the treatment of PBC.
- Patients and method: Twenty-four patients diagnosed with PBC by liver biopsy were enrolled. Half randomly assigned to bezafibrate 400mg/day (all women, average age 60.3 ± 6.5 years, range 48-69 years) and half UDCA 600mg/day (one man, eleven women, average age 59.8 ±.2yr, range 48-68years).
  Both drugs were taken for 12 months
  All clinical laboratory results (ALT, ALP, Y-GTP and IgM) were recorded at 1, 3, 6 and 12 months of treatment, with comparison to pre-treatment levels.
- Results: All clinical laboratory results decreased significantly at 1, 3, 6, and 12 months in the bezafibrate group compared with pre-treatment levels.
  All clinical laboratory test results also decreased significantly in the UDCA group, although patients in the bezafibrate group showed more highly significant reductions than those in the UDCA group for all test results at 1, 3, 6, and 12 months.
  No adverse reactions were observed in either group.

Study: Iwasaki et al.,1999. Bezafibrate may have a beneficial effect in pre-cirrhotic primary biliary cirrhosis (PBC):

- Objective: To evaluate the efficacy of bezafibrate in primary biliary cirrhosis.
- Patients and methods:
  11 pre-cirrhotic PBC patients were enrolled for 12–21 months.
  Participants were aged 55-74.
  Of the 11 patients: 9 had been previously given 600mg/day UDCA for a year or more that had not shown normalisation of biliary enzymes prior to the study. Of these:
  7 were given 400mg/day bezafibrate concomitantly with UCDA.
  2 were given 400mg/day bezafibrate alone after UDCA discontinuation.
  Final 2 were given 400mg/day bezafibate alone from the start.
  4 patients in the cohort were symptomatic – 2 patients had pruritus and chronic fatigue, and 2 chronic fatigue
- Results: Pruritus and chronic fatigue gradually disappeared in all 4 symptomatic patients within two months after the start of the therapy.
  In all patients biliary enzymes, ALP and γ-glutamyltransferase (γ-GTP) levels have significantly decreased by 47.5–71.0% (mean 62.0%) and 29.5–78.4% (mean 43.7%), respectively. They decreased rapidly in first 2 months, and then gradually reached the plateau.
  Looking at each group of patients specifically:
  In all 7 patients treated with UDCA prior to the study (but not shown a significant response), and administered bezafibrate and UDCA within the study showed significantly reduced biliary enzymes and transaminases. In 3 patients biliary enzymes normalized.
  In the 2 patients treated with UDCA prior to the study (but not showing a significant response), and given bezafibrate without UDCA, also brought better responses.
  The final 2 patients that only received bezafibrate from the start showed normalisation of ALP.
- Conclusion: Results indicate that bezafibrate has an additional effect to UDCA therapy in pre-cirrhotic PBC patients and may have independent beneficial effects.

Safety (from the manufacturers summaries of product characteristics):

- Bezafibrate
  Common side effects: reduced appetite, gastrointestinal disorders.
  Uncommon side effects: AKI, alopecia, erectile dysfunction, constipation, diarrhoea, cholestasis, muscle complaints/weakness (manifestation of myopathy), headache, nausea, photosensitivity and skin reactions
  Monitoring: liver function and creatinine kinase when fibrates are used with statins
  Overdose: No specific effects of acute overdose are known (apart from rhabdomyolysis). There is no specific antidote. Thus appropriate symptomatic therapy is recommended in cases of overdose. In cases of rhabdomyolysis, bezafibrate must be stopped immediately and renal function carefully monitored.

- Fenofibrate
  Side Effects
  Common side effects: Digestive, gastric or intestinal disorders (abdominal pain, nausea, vomiting, diarrhoea, and flatulence) moderate in severity

Uncommon side effects: cholelithiasis, embolism/thrombosis, headache, muscle complaints/ weakness (manifestation of myopathy), pancreatitis, sexual dysfunction and skin reactions.
Monitoring: Manufacturer advises monitor hepatic transaminases every 3 months during the first 12 months of treatment and periodically thereafter—discontinue treatment if levels increase to more than 3 times the upper limit of normal; monitor serum creatinine levels during the first 3 months of treatment and periodically thereafter—interrupt treatment if creatinine level is 50% above the upper limit of normal.
Overdose: No case of over dosage has been reported. No specific antidote is known. If an overdose is suspected, treat symptomatically and institute appropriate supportive measures as required.

Cost of treatment and Cost Effectiveness:

- No cost effectiveness evidence is available for fibrates in this indication, potentially due to ''off-label' use.
- Costs below are for general comparison only and do not imply therapeutic equivalence.
- Table summarising treatment prices and annual cost per patient including licensed products (ursodeoxycholic acid and obeticholic acid):

Drug	Dose	Pack size	Price	Estimated annual cost per patient
Bezafibrate 200mg tablets	200mg TDS	100 tablets	£8.63	£95
Bezafibrate 400mg MR tablets	400mg OD	30 tablets	£7.63	£93
Fenofibrate 160mg micronised tablets	160mg OD	28 tablets	£3.98	£52
Ursodeoxycholic acid*	Varies based on weight	varies	£29.48	£1793
Obeticholic acid 5mg capsules^	Varies based on weight	30 capsules	NOT STATED[a]	NOT STATED[a]
Obeticholic acid 10mg capsules^	Varies based on weight	30 capsules	NOT STATED[a]	NOT STATED[a]

*There are a range of product strengths (150mg, 250mg, 300mg etc.) available and the dose is weight based, hence an average product cost and weight have been used to estimate annual costs.
^dosing range varies depending on hepatic status of the patient, ranging from daily dosing to once weekly dosing.
[a] **This cost is a simple patient access scheme discount price. This information is commercial in confidence and is not for publication**
For the proposed place in therapy it is uncertain what the cost pressure of extending the pathway to allow use of fibrates as exact patient numbers are not known.

The needs of the population:

- The needs of the population would be low as there are alternative licensed treatment options which are established in clinical practice.
- Specialists have indicated that it may be beneficial however the trial evidence is limited

The needs of the community:

- The needs of the community are uncertain as the estimated patient numbers are not known.
- There will be an increase in prescribing costs when initiating as an add on treatment, however when prescribed instead of UDCA or OCA prescribing costs would decrease.

Equity and Equality:

- No impact anticipated. Guidance applies to all relevant patients where indicated. There is no differential impact expected on one or more equality groups differently to others Age, Disability; Gender reassignment; Marriage & Civil Partnership; Pregnancy & Maternity; Race; Religion & Belief; Sex; Sexual orientation.

Policy drivers:

- **National drivers:**
  - **NICE:** No decision/guidance in place
  - **Scottish Medicines Consortium:** No decision/guidance in place
  - **All Wales Medicines Strategy Group (AWMSG):** No decision/guidance in place
  - **The British Society of Gastroenterology/UK-PBC treatment and management guidelines:**
    - Recommends first line use of oral UDCA in all patients with PBC and if tolerated should be continued lifelong
    - Recommends use of OCA in line with NICE TAG 443:
      It is recommended, within its marketing authorisation, as an option for treating primary biliary cholangitis in

combination with UDCA for people whose disease has responded inadequately to UDCA or as monotherapy for people who cannot tolerate UDCA. OCA is recommended only if the company provides it with the discount agreed in the patient access scheme.
Assess the response to obeticholic acid after 12 months. Only continue if there is evidence of clinical benefit
- In the 'off label' therapies section it states that fibrates have not gained much traction in the UK and a meta-analysis of existing bezafibrate randomised clinical trials show no significant improvement in patient survival compared with UDCA monotherapy.
- Fibrates have not been included in the consensus care pathway as a treatment option.

➢ **EoE CCG decisions:** No decisions found

➢ **Other:**
- **European Association for the Study of the Liver (EASL) guidelines:**
  - Includes second line 'off label' fibrates as an add on therapy option to UDCA non-responders alongside the alternative, licensed OCA.

Implementability:
Requires engagement from primary, community and secondary care to ensure consistency across local health economies

References:

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- NICE TA443 Obeticholic acid for treating primary biliary cholangitis Published date: 26 April 2017 https://www.nice.org.uk/guidance/ta443
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