Patient Advocacy Group Collective Statement

On Fri 28 June 2024, the European Medicines Agency (EMA) made a recommendation to revoke the license of Obeticholic Acid (OCA) for use in PBC in the EU. We, the PBC patient community, are asking the European Commission (EC), in the strongest possible terms, not to accept that recommendation.

We, the patients, have concerns about EMA's process and to what degree it looked at real world evidence. The real world evidence is clear that, when used appropriately in PBC, OCA is a helpful tool for patients with PBC, particularly to those who are not served by any other medication.

The EMA recommendation sets a number of precedents that are potentially dangerous for the PBC patient community:

1) In a rare disease, in high risk patients, use of placebo arm trials when medication is available is a life-expectancy risk to patients and, as such, is unethical, unachievable, and unable to answer the questions set, COBALT being one such example
2) Unrealistic goals of evidence, reliant on placebo trials and ignoring real world evidence, will be a barrier to future treatments: not only in PBC but in a number of rare diseases in the future
3) PBC patients have stated they would rather be itchy, albeit that is a relatively small risk in the long-term use of OCA, than be at risk of disease progression, liver transplant or death due to untreated disease[1]
4) There are three current mechanisms for PBC treatment: UDCA, a naturally occurring hydrophilic bile acid; OCA, an FXR agonist; and PPAR agonists (both repurposed drugs and potentially new treatments).[2] Many patients rely on triple therapy for liver biochemistry to normalise
5) ALP reduction in PBC is almost universally accepted as beneficial in PBC, irrespective of mechanism[2], and OCA has shown in real world evidence that it can have a profound effect on ALP in patients in whom UDCA has not made a significant difference.[2]
6) Many patients suffering from impaired renal function or have experienced fibrate-based liver toxicity cannot take fibrates (off-label).[3] Due to its different mechanism, OCA is the only option for these patients if ursodeoxycholic acid does not respond sufficiently.[4]

Patients acknowledge OCA is not the single answer to PBC, but know it has shown significant benefit over a number of years to a significant proportion of patients. UDCA is licensed and is reliant on real world evidence for its continuation as a therapy. PBC is a long-term condition so it will take many years to prove the effectiveness of OCA, just as it did with UDCA.

We are asking that clinicians have the option to use OCA for patients in need and that it is readily available as a licensed therapy for use in PBC.

Please, on behalf of patients today and tomorrow, allow this license to continue- even if conditionally on more real world evidence to be shown- in PBC.

Signed,

[1] Hirschfield, G. M., Dyson, J. K., Alexander, G. J., Chapman, M. H., Collier, J., Hübscher, S., … & Jones, D. E. (2018). The British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines. *Gut*, 67(9), 1568-1594. doi:10.1136/gutjnl-2017-315259.

[2] Lindor, K. D., Bowlus, C. L., Boyer, J., Levy, C., & Mayo, M. (2019). Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases. *Hepatology*, 69(1), 394-419. doi:10.1002/hep.30145.

[3] European Association for the Study of the Liver (EASL). (2017). EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. *Journal of Hepatology*, 67(1), 145-172. doi:10.1016/j.jhep.2017.03.022.

[4] Nevens, F., Andreone, P., Mazzella, G., Strasser, S. I., Bowlus, C. L., Invernizzi, P., … & Jones, D. E. (2016). A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis. *New England Journal of Medicine*, 375(7), 631-643. doi:10.1056/NEJMoa1509840.