

Filed Pursuant to Rule 433 Issuer Free Writing Prospectus dated May 31, 2023 Relating to Preliminary Prospectus Supplement dated May 31, 2023 Registration Statement No. 333-258564

NEWS RELEASE

FOR IMMEDIATE RELEASE

LEXICON ANNOUNCES PROPOSED PUBLIC OFFERING OF COMMON STOCK

The Woodlands, Texas, May 31, 2023 – Lexicon Pharmaceuticals, Inc. (Nasdaq: LXRX) ("*Lexicon*") today announced that it has commenced an underwritten public offering to offer and sell, subject to market and other conditions, shares of its common stock, par value \$0.001. In addition, Lexicon intends to grant the underwriters a 30-day option to purchase additional shares of common stock. There can be no assurance as to whether or when the proposed offering may be completed, or as to the actual size or terms of the proposed offering.

Citigroup, Jefferies and Piper Sandler are acting as joint book-running managers for the proposed offering.

Concurrently with the closing of the underwritten public offering, Lexicon intends to sell shares of its common stock in a private placement to an affiliate of Invus, L.P., Lexicon's largest stockholder, pursuant to its preemptive right under Lexicon's Fifth Amended and Restated Certificate of Incorporation. Lexicon intends to grant the private placement purchaser an option to purchase, on a pro rata basis, additional shares of common stock to the extent the underwriters exercise their option to purchase additional common stock. Any shares of common stock offered pursuant to the concurrent private placement would not be registered under the Securities Act of 1933, as amended (the "Securities Act"). The closing of the underwritten public offering is not conditioned on the closing of the concurrent private placement.

Lexicon currently intends to use the net proceeds that it will receive from the proposed offering, together with its existing cash and cash equivalents and short-term investments, to fund the commercial launch of INPEFA™ (sotagliflozin). Lexicon expects to use any remaining net proceeds that it will receive from the proposed offering to fund the continued research and development of its drug candidates and for working capital and other general corporate purposes.

A shelf registration statement on Form S-3 relating to the proposed offering was filed with the U.S. Securities and Exchange Commission ("SEC") on August 6, 2021 and declared effective by the SEC on September 14, 2021 (File No. 333-258564). A preliminary prospectus supplement and accompanying prospectus relating to the proposed offering will be filed with the SEC and will be available on the SEC's website at www.sec.gov. When available, copies of the preliminary prospectus supplement and accompanying prospectus may also be obtained from Citigroup, c/o Broadridge Financial Services, 1155 Long Island Avenue, Edgewood, NY 11717 (Tel: 800-831-9146); Jefferies LLC, Attention: Equity Syndicate Prospectus Department, 520 Madison Avenue, New York, NY 10022, by e-mail at prospectus department@jefferies.com or by telephone at (877) 821-7388; or Piper Sandler & Co., Attention: Prospectus Department, 800 Nicollet Mall, J12S03, Minneapolis, Minnesota 55402, by telephone at (800) 747-3924, or by email at prospectus@psc.com.

This press release does not constitute an offer to sell, or the solicitation of an offer to buy, these securities, nor will there be any sale of these securities in any state or jurisdiction in which such offer, solicitation or sale is not permitted.

About Lexicon Pharmaceuticals

Lexicon is a biopharmaceutical company with a mission of pioneering medicines that safely and effectively treat disease. Lexicon advanced two of these medicines to market and has additional drug candidates in discovery and clinical and preclinical development in heart failure, neuropathic pain, diabetes and metabolism and other indications.

Safe Harbor Statement

This press release contains "forward-looking statements" within the meaning of Section 27A of the Securities Act and Section 21E of the Securities Exchange Act of 1934, as amended. All forward-looking statements, including, without limitation, statements about the completion and timing of the proposed offering, the use of proceeds from the proposed offering and the grant of the option to the underwriters and the private placement purchaser to purchase additional shares, are based on management's current assumptions and expectations and involve risks, uncertainties and other important factors, specifically including Lexicon's ability to meet its capital requirements, successfully commercialize INPEFA in heart failure on the timeline and/or at the prices currently contemplated or at all, conduct preclinical and clinical development and obtain necessary regulatory approvals of INPEFA (in other indications), LX9211 and its other drug candidates on its anticipated timelines, achieve its operational objectives, obtain patent protection for its discoveries and establish strategic alliances, as well as additional factors relating to manufacturing, intellectual property rights, and the therapeutic or commercial value of its drug candidates. Any of these risks, uncertainties and other factors may cause Lexicon's actual results to be materially different from any future results expressed or implied by such forward-looking statements. Information identifying such important factors is contained under "Risk Factors" in Lexicon's annual report on Form 10-K for the year ended December 31, 2022, quarterly report on Form 10-Q for the quarter ended March 31, 2023 and other subsequent disclosure documents filed with the SEC. Lexicon undertakes no obligation to update or revise any such forward-looking statements, whether as a result of new information, future events or otherwise.

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Registration Statement

Lexicon has filed a registration statement (including a prospectus) with the SEC for the equity offering to which this communication relates. Before you invest, you should read the preliminary prospectus supplement and the accompanying prospectus in that registration statement and other documents Lexicon has filed with the SEC for more complete information about Lexicon and the equity offering. You may get these documents for free by visiting EDGAR on the SEC's website at www.sec.gov. When available, copies of the preliminary prospectus supplement and accompanying prospectus may also be obtained from Citigroup, c/o Broadridge Financial Services, 1155 Long Island Avenue, Edgewood, NY 11717 (Tel: 800-831-9146); Jefferies LLC, Attention: Equity Syndicate Prospectus Department, 520 Madison Avenue, New York, NY 10022, by e-mail at prospectus_department@jefferies.com or by telephone at (877) 821-7388; or Piper Sandler & Co., Attention: Prospectus Department, 800 Nicollet Mall, J12S03, Minneapolis, Minnesota 55402, by telephone at (800) 747-3924, or by email at prospectus@psc.com.