



April 28, 2016

✓ **BSE Limited,**  
Department of Corporate Services,  
P. J. Towers, Dalal Street,  
Mumbai Samachar Marg,  
**MUMBAI - 400 001.**

**The National Stock Exchange of India Ltd.,**  
Exchange Plaza,  
Bandra Kurla Complex,  
Bandra (East),  
**MUMBAI - 400 051.**

Dear Sir,

**Sub: Disclosure pursuant to Regulation 30 of the SEBI (Listing Obligations and Disclosure Requirements) Regulations, 2015.**

Enclosed is a press release as regards re-introduction by the Company of Methergine® (methylergonovine maleate) Oral Tablets 0.2mg for the prevention and management of postpartum hemorrhage (PPH). Methergine® is the only FDA-approved oral uterotonic and is a preferred oral agent in the management of PPH, according to guidelines issued by the American Congress of Obstetricians and Gynecologists.

This may be considered as a disclosure pursuant to Regulation 30 of the SEBI (Listing Obligations and Disclosure Requirements) Regulations, 2015.

Thanking you,

Yours faithfully,  
For **LUPIN LIMITED**

**R. V. SATAM**  
**COMPANY SECRETARY & COMPLIANCE OFFICER**

Encl: a/a



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## Lupin Bolsters US Brands Portfolio with Methergine® Oral Tablets *Product to Address Rising Incidence of Postpartum Hemorrhage in the US*

*The only FDA-approved oral uterotonic for the management of PPH, comes to market with a significant investment in professional medical education to improve care*

**Mumbai, Baltimore, April 28, 2016:** Pharma Major Lupin Limited and its US subsidiary, Lupin Pharmaceuticals, Inc. (collectively Lupin) have announced the re-introduction of Methergine® (methylergonovine maleate) Oral Tablets 0.2mg for the prevention and management of postpartum hemorrhage (PPH). Methergine® is the only FDA-approved oral uterotonic and is a preferred oral agent in the management of PPH<sup>i</sup>, according to guidelines issued by the American Congress of Obstetricians and Gynecologists (ACOG)<sup>ii</sup>. More than half of all maternal deaths occur within 24 hours of birth, most commonly from excessive bleeding<sup>iii</sup>, and rates of maternal mortality continue to rise in the US<sup>iv</sup> where PPH is a leading cause of pregnancy complications<sup>v</sup>.

“The re-introduction of Methergine is a proud moment for Lupin, but also an important moment for expectant mothers across the country to feel confident in care options,” said Paul McGarty, President, Lupin Pharmaceuticals Inc. “With Methergine, Lupin is making a significant investment to help improve the management of PPH, providing professional medical education, leveraging its specialized sales force to drive better awareness and access to care, and ensuring a more stable supply of this essential medicine.”

One area of need is further physician education around ascertaining accurate blood loss -- a barrier to optimal care. PPH is defined as blood loss in excess of 500 mL after vaginal delivery or 1000 mL after cesarean delivery<sup>vi</sup>, and according to the Association of Women’s Health Obstetric and Neonatal Nurses, visual estimation of blood loss is consistently underestimated for volumes over 1000 mL and usually overestimated for smaller volumes<sup>vii</sup>. Underestimation of blood loss can lead to the delay of life-saving interventions, while overestimation can lead to costly, unnecessary treatments, such as blood transfusions.<sup>viii</sup>

“Postpartum hemorrhage (PPH) is one of the most preventable causes of maternal mortality and it should be better managed in pursuit of improved patient care,” said David B. Schwartz, MD, FACOG, independent OBGYN and ACOG fellow. “I commend Lupin for spotlighting this public health issue and making an investment in treatment, education and awareness of PPH.”

A semi-synthetic ergot alkaloid, Methergine is indicated for routine management of uterine atony, hemorrhage and subinvolution of the uterus following delivery of the placenta, and for control of uterine hemorrhage in the second stage of labor following delivery of the anterior shoulder. Methergine provides specific and rapid (onset of action under 10 minutes) uterotonic action on the smooth muscle of the uterus to increase contractions, resulting in restricting blood loss.

The Methergine dosing schedule is one tablet (0.2 mg) three or four times daily in the puerperium for a maximum of one week. The most common adverse event is hypertension associated in several cases with seizure and/or headache. Methylergonovine maleate is available as an intramuscular injection or as an oral tablet; Lupin acquired oral methylergonovine maleate earlier this year.



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For more information about Methergine, visit [www.Methergine.com](http://www.Methergine.com).

### **About Postpartum Hemorrhage (PPH)**

Postpartum hemorrhage (PPH) is often defined as blood loss in excess of 500 mL after vaginal delivery or 1000 mL after cesarean delivery.<sup>ix</sup> It is generally classified as primary – occurring within the first 24 hours of delivery – or secondary, up to 6-12 weeks postpartum.<sup>x</sup>

PPH is a leading cause of birth complications, and it is estimated that 2.9% of the women who give birth in the United States will bleed too much.<sup>xi</sup> In the past decade, there has been a 183% increase in the number of women receiving a blood transfusion around the time they gave birth.<sup>xii</sup> It is estimated that, worldwide, 140,000 women die of postpartum hemorrhage each year -- one every four minutes.<sup>xiii</sup> The US is ranked 47th in the world for maternal mortality.<sup>xiv</sup>

Causes of postpartum hemorrhage include uterine atony, retained placenta, placenta accreta, defects in coagulation, and uterine inversion while secondary causes include subinvolution of placental site, retained products of conception, infection and inherited coagulation defects.<sup>xv,xvi,xvii,xviii,xix,xx</sup> Uterine atony accounts for 79% of the cases of PPH.<sup>xxi</sup> Patient risk factors for postpartum hemorrhage include labor induction and augmentation, current or prior cesarean delivery, history of postpartum hemorrhage, hypertensive disorder of pregnancy, fibroids, placenta previa, coagulopathy, and obesity.<sup>xxii,xxiii</sup> Women of Hispanic and Asian descent have an increased risk of postpartum hemorrhage.<sup>xxiv</sup>

### **About Lupin Limited**

Headquartered in Mumbai, Lupin is an innovation led transnational pharmaceutical company producing and developing a wide range of branded & generic formulations, biotechnology products and APIs globally. The Company is a significant player in the Cardiovascular, Diabetology, Asthma, Pediatric, CNS, GI, Anti-Infective and NSAID space and holds global leadership positions in the Anti-TB and Cephalosporin segment.

Lupin is the 5<sup>th</sup> largest generics player in the US (5.6% market share by prescriptions, IMS Health) and amongst the fastest growing top 10 generic pharmaceutical players in Japan (ranked 9<sup>th</sup>) and South Africa (ranked 4<sup>th</sup> – IMS Health). For the financial year ended 31st March 2015, Lupin's Consolidated Turnover and Profit after Tax were Rs. 125,997 million (USD 2.06 billion) and Rs. 24,032 million (USD 393 million) respectively. Please visit <http://www.lupin.com> for more information.

### **About Lupin Pharmaceuticals Inc. (LPI)**

Headquartered in Baltimore, Maryland, Lupin Pharmaceuticals, Inc. is dedicated to delivering high-quality, affordable specialty and generic medicines trusted by healthcare professionals and patients in the United States. Lupin has been a trusted partner in the US women's health space, providing medicine to patients across a range of products which includes oral contraceptives and medications that treat postmenopausal osteoporosis and vasomotor symptoms due to menopause. Please visit <http://www.lupinpharmaceuticals.com> for more information.

You could also follow us on Twitter – [www.twitter.com/lupinlimited](http://www.twitter.com/lupinlimited)



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*[\\*Safe Harbor Statement](#)*

*Methergine® is a registered trademark of Novartis AG.*

**Important Safety Information for Methergine®**

**METHERGINE® TABLETS**

**Important Safety Information**

Methergine Tablets are contraindicated for patients with the following conditions: hypertension, toxemia, pregnancy, and hypersensitivity.

**WARNINGS**

**General:** This drug should not be administered I.V. routinely because of the possibility of inducing sudden hypertensive and cerebrovascular accidents. If I.V. administration is considered essential as a lifesaving measure, Methergine (methylergonovine maleate) should be given slowly over a period of no less than 60 seconds with careful monitoring of blood pressure. Intra-arterial or periarterial injection should be strictly avoided. Caution should be exercised in presence of impaired hepatic or renal function.

**Breast-feeding:** Mothers should not breast-feed during treatment with Methergine. Milk secreted during this period should be discarded. Methergine may produce adverse effects in the breast-feeding infant. Methergine may also reduce the yield of breast milk. Mothers should wait at least 12 hours after administration of the last dose of Methergine before initiating or resuming breast feeding.

**Coronary artery disease:** Patients with coronary artery disease or risk factors for coronary artery disease (e.g., smoking, obesity, diabetes, high cholesterol) may be more susceptible to developing myocardial ischemia and infarction associated with methylergonovine-induced vasospasm.

**Medication errors:** Inadvertent administration of Methergine to newborn infants has been reported. In these



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cases of inadvertent neonatal exposure, symptoms such as respiratory depression, convulsions, cyanosis and oliguria have been reported. Usual treatment is symptomatic. However, in severe cases, respiratory and cardiovascular support is required. Methergine has been administered instead of vitamin K and Hepatitis B vaccine, medications which are routinely administered to the newborn. Due to the potential for accidental neonatal exposure, Methergine injection should be stored separately from medications intended for neonatal administration.

#### PRECAUTIONS

**General:** Caution should be exercised in the presence of sepsis, obliterative vascular disease. Also use with caution during the second stage of labor. The necessity for manual removal of a retained placenta should occur only rarely with proper technique and adequate allowance of time for its spontaneous separation.

**Drug Interactions:** There have been rare reports of serious adverse events in connection with the co-administration of certain ergot alkaloid drugs (e.g., dihydroergotamine and ergotamine) and potent CYP 3A4 inhibitors, resulting in vasospasm leading to cerebral ischemia and/or ischemia of the extremities.

Caution should be exercised when Methergine® Tablets are used concurrently with beta-blockers. Concomitant administration with beta-blockers may enhance the vasoconstrictive action of ergot alkaloids.

#### ADVERSE REACTIONS

The most common adverse reaction is hypertension associated in several cases with seizure and/or headache. Hypotension and anaphylaxis has also been reported. Cerebrovascular accident, paraesthesia, ventricular fibrillation, ventricular tachycardia, angina pectoris, atrioventricular block were also reported post-marketing.

Safety and effectiveness in pediatric patients have not been established.

**You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch), or call 1-800-FDA-1088, or call Lupin Pharmaceuticals, Inc. at 1-800-399-2561.**

**Please note that this information is not comprehensive. Please see the full prescribing Information at [www.methergine.com](http://www.methergine.com)**

<sup>i</sup> Bateman BT, Tsen LC, Liu J, Butwick AJ, Huybrechts KF. Patterns of Second-Line Uterotonic Use in a Large Sample of Hospitalizations for Childbirth in the United States: 2007–2011. *Anesth Analg*. 2014;119(6):1344-9.

<sup>ii</sup> ACOG Practice Bulletin. Optimizing Protocols in Obstetrics: Management of Obstetric Hemorrhage. October 2006:108(4); ACOG Practice Bulletin 135. Second-trimester abortion. *Obstet Gynecol*. 2013;121:1394-1406.

<sup>iii</sup> ACOG Practice Bulletin. Optimizing Protocols in Obstetrics: Management of Obstetric Hemorrhage. October 2006:108(4).

<sup>iv</sup> Ahmadzia HK, Grotegut C, James A. Poster Session III: 509 - Rates of postpartum hemorrhage and related interventions: United States, 2000-2012. *AJOG*. 2016;214(1):S277.

<sup>v</sup> The AWHONN Postpartum Hemorrhage Project. 2013. <http://www.pphproject.org/maternal-morbidity-mortality.asp>

<sup>vi</sup> ACOG Practice Bulletin. Optimizing Protocols in Obstetrics: Management of Obstetric Hemorrhage. October 2006:108(4); ACOG Practice Bulletin 135. Second-trimester abortion. *Obstet Gynecol*. 2013;121:1394-1406.

<sup>vii</sup> AWHONN Practice Brief. Quantification of Blood Loss. *JOGNN*. 2014:1-3. DOI: 10.1111/1552-6909.12519

<sup>viii</sup> AWHONN Practice Brief. Quantification of Blood Loss. *JOGNN*. 2014:1-3. DOI: 10.1111/1552-6909.12519

<sup>ix</sup> ACOG Practice Bulletin. Optimizing Protocols in Obstetrics: Management of Obstetric Hemorrhage. October 2006:108(4).

<sup>x</sup> ACOG Practice Bulletin. Optimizing Protocols in Obstetrics: Management of Obstetric Hemorrhage. October 2006:108(4).

<sup>xi</sup> The AWHONN Postpartum Hemorrhage Project. 2013. <http://www.pphproject.org/maternal-morbidity-mortality.asp>

<sup>xii</sup> Bateman et al. The Epidemiology of PPH in a Large, Nationwide Sample of Deliveries. *Anesthesia & Analgesia*. 2010;110(5):1368-73.

<sup>xiii</sup> ACOG Practice Bulletin. Optimizing Protocols in Obstetrics: Management of Obstetric Hemorrhage. October 2006:108(4).



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<sup>xiv</sup> The AWHONN Postpartum Hemorrhage Project. 2013. <http://www.pphproject.org/maternal-morbidity-mortality.asp>

<sup>xv</sup> Al-Zirqi I, Vangen S, Forsen L, Stray-Pedersen B. Prevalence and risk factors of severe obstetric haemorrhage. *BJOG*. 2008 Sep;115(10):1265-72.

<sup>xvi</sup> Berg CJ, Callaghan WM, Syverson C, Henderson Z. Pregnancy-related mortality in the United States, 1998 to 2005. *Obstet Gynecol*. 2010 Dec;116(6):1302-9.

<sup>xvii</sup> Chichakli LO, Atrash HK, MacKay AP, Musani AS, Berg CJ. Pregnancy-related mortality in the United States due to hemorrhage: 1979-1992. *Obstet Gynecol*. 1999 Nov;94(5 Pt 1):721-5.

<sup>xviii</sup> Abrams ET, Rutherford JN. Framing postpartum hemorrhage as a consequence of human placental biology: an evolutionary and comparative perspective. *Am Anthropol*. 2011;113(3):417-30.

<sup>xix</sup> Bateman BT, Berman MF, Riley LE, Leffert LR. The epidemiology of postpartum hemorrhage in a large, nationwide sample of deliveries. *Anesth Analg*. 2010 May 1;110(5):1368-73.

<sup>xx</sup> ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists Number 76, October 2006: postpartum hemorrhage. American College of Obstetricians and Gynecologists. *Obstet Gynecol*. 2006 Oct;108(4):1039-47.

<sup>xxi</sup> Bateman BT, Berman MF, Riley LE, Leffert LR. The epidemiology of postpartum hemorrhage in a large, nationwide sample of deliveries. *Anesth Analg*. 2010 May 1;110(5):1368-73.

<sup>xxii</sup> Oyelese Y, Ananth CV. Postpartum hemorrhage: epidemiology, risk factors, and causes. *Clin Obstet Gynecol*. 2010 Mar;53(1):147-56.

<sup>xxiii</sup> Blomberg M. Maternal obesity and risk of postpartum hemorrhage. *Obstet Gynecol*. 2011 Sep;118(3):561-8.

<sup>xxiv</sup> Bryant A, Mhyre JM, Leffert LR, Hoban RA, Yakoob MY, Bateman BT. The association of maternal race and ethnicity and the risk of postpartum hemorrhage. *Anesth Analg*. 2012 Nov;115(5):1127-36.

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