

## PRODUCT DATA SHEET

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### Metformin powered by Lipodisq™ Sterile Solution

Nano-formulated aqueous solution: Ready-to-use

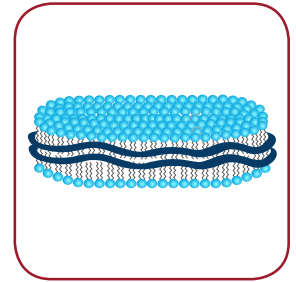
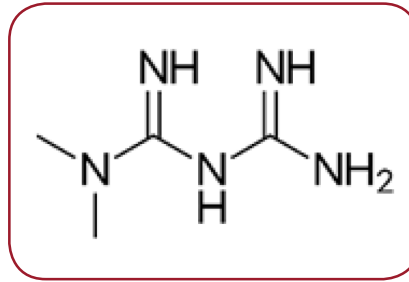
**Cat. No.:** IAX-700-103

**Lot. No.:**

<b>Synonyms</b>	Dimethylbiguanide in a detergent-free nano-formulation made of styrene-maleic acid lipid particles (SMALP)
<b>Empirical Formula</b>	C <sub>4</sub> H <sub>11</sub> N <sub>5</sub> · HCl
<b>Concentration</b>	1 mg/ml (0.1% w/vol)
<b>Size</b>	1 ml
<b>MW</b>	129.2 · 36.5
<b>CAS</b>	1115-70-4
<b>Purity</b>	≥ 95% (HPLC)
<b>Solution pH</b>	7.00 - 7.50
<b>Solubility</b>	Soluble in water, PBS, Tris and other physiological solutions as formulated in a proprietary, thermostable, aqueous lipid nanoparticulate formulation (Lipodisq™, Malvern Cosmeceutics Ltd., Malvern UK). Avoid the use of buffers with divalent ions such as Ca or Mg or pH <6.5 or >8.0, which can cause particle instability. Unformulated metformin is soluble in water or DMSO.
<b>Formulation</b>	Lipodisq™ are nanosized lipid-based discoidal particles that can be manufactured to incorporate hydrophobic, poorly water-soluble compounds, such as lipids, lipoproteins and glycolipids.
<b>Appearance</b>	Colourless clear aqueous solution
<b>Handling</b>	Keep sterile. Avoid skin and eye contact.
<b>Activity</b>	Cell culture tested (human macrophage cell line) (MTT). Recommended starting dilution: 1:200 or higher. Optimal working concentrations depend on the applications and need to be determined. Published procedures using Lipodisq™ formulations (Curcumin and IAXO TLR4 antagonists) <i>in vivo</i> rodent models at 3-10mg/kg. Recommended route of administration is subcutaneous (s.c.) with oral or nasal application as a possible alternative, which needs to be optimised. Carrier only control: Lipodisq™ Control Sterile Solution (Cat. No.: IAX-700-100).
<b>Shipping</b>	Ambient
<b>Storage</b>	2-8°C
<b>Stability</b>	12 months after receipt (unopened and as supplied)
<b>MSDS</b>	Available on request

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#### General Information

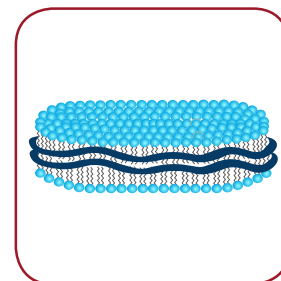
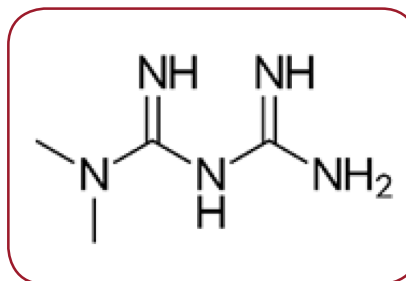
- Metformin is an antihyperglycemic agent of the biguanide class, used for the management of type II diabetes and is currently prescribed to at least 120 million people worldwide.
- AMPK activator
- Mitochondrial electron transport chain complex I inhibitor, reducing mitochondrial reactive oxygen species (ROS).
- Antidiabetic and anti-hyperglycemic agent that reduces blood glucose levels, improves insulin sensitivity, and decreases insulin resistance.
- Insulin sensitizer in non-alcoholic fatty liver disease (NAFLD).
- Increases plasma concentrations of the glucose-lowering gut incretin hormone glucagon-like peptide-1 (GLP-1), which may contribute to metformin's glucose-lowering effect.
- Anticancer agent with antiproliferative and proapoptotic activity in cancer cell lines.
- Autophagy activator
- Targets brown adipose tissue (BAT) in vivo and reduces oxygen consumption.
- Anti-inflammatory agent by inhibition of nuclear factor κB (NF-κB) via AMPK-dependent and independent pathways. Also described to inhibit NLRP3 inflammasome activation, subsequent caspase-1 cleavage and interleukin-1β secretion.
- Since the emergence of SARS-CoV-2, Metformin has been investigated as a prophylactic agent for the prevention of COVID-19.

#### Metformin References

- [1] *Cellular and molecular mechanisms of metformin: an overview.* Viollet B, et al. Clin. Sci. (2012); 122:253-70
- [2] *Metformin Use Is Associated With Reduced Mortality in a Diverse Population With COVID-19 and Diabetes.* Crouse AB, et al. Front. Endocrinol. (2021); 11:600439
- [3] *Metformin in 2019.* Flory J, Lipska K. JAMA (2019); 321:1926
- [4] *Metformin inhibition of mitochondrial ATP and DNA synthesis abrogates NLRP3 inflammasome activation and pulmonary inflammation.* Flory J, and Lipska K. Immunity (2021); 54:1463
- [5] *Metformin and Covid-19: Focused Review of Mechanisms and Current Literature Suggesting Benefit.* Ibrahim S, et al. JAMA (2019); 321:1926
- [6] *Metformin in Patients With COVID-19: A Systematic Review and Meta-Analysis.* Front. Med. (2021); 8:704666
- [7] *Outpatient metformin use is associated with reduced severity of COVID-19 disease in adults with overweight or obesity.* CT, et al. J. Med. Virol. (2021); 93:4273
- [8] *Metformin inhibition of mitochondrial ATP and DNA synthesis abrogates NLRP3 inflammasome activation and pulmonary inflammation.* Xian H, et al. Immunity (2021); 54:1463
- [9] *Metformin and Covid-19: Focused Review of Mechanisms and Current Literature Suggesting Benefit.* Ibrahim S, et al. Front. Endocrinol. (2021); 12:587801

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#### Lipodisq™ Technology

- A nanoparticle (11-40nm) drug delivery system comprising a discoidal phospholipid bilayer membrane stabilised by a chaperone molecule annulus.
- Internal properties of the phospholipid membrane support the disposition and stabilisation of drug molecule candidates and preserve the native conformation of membrane molecules.
- The resulting encapsulated actives are rendered water-soluble and specialised for intra-cellular penetration/delivery via endosomal uptake mechanisms.
- Lipodisq™ solutions show a good safety profile and are suitable for *in vitro* and *in vivo* investigations.
- For a customizable biodegradable Lipodisq™ version with a higher concentration of actives or an alternative lipid option, contact Innaxon.

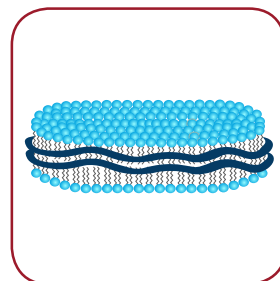
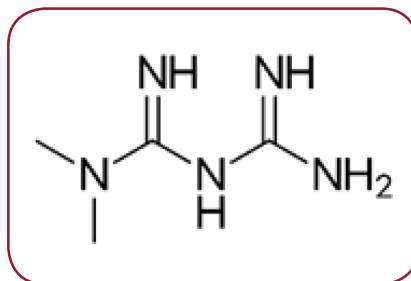
Component	Concentration	CAS #	EC #
Water (sterile)	QS	7732-18-5	231-791-2
Poly(styrene maleic acid)	25mg/ml	26762-29-8	607-996-1
Lecithin	9mg/ml	92128-87-5	295-786-7
Metformin hydrochloride	1 mg/ml	1115-70-4	214-230-6

#### Lipodisq™ References

- [1] *Mechanisms of Formation, Structure, and Dynamics of Lipoprotein Discs Stabilized by Amphiphilic Copolymers: A Comprehensive Review.* Orekhov PS, et al. *Nanomaterials* (2022); 12:361
- [2] *Applications of Synthetic Polymer Discoidal Lipid Nanoparticles to Biomedical Research.* Tanaka M. *Chem. Pharm. Bull.* (2022); 70:507
- [3] *Understanding the Structural Pathways for Lipid Nanodisc Formation: How Styrene Maleic Acid Copolymers Induce Membrane Fracture and Disc Formation.* Bjørnstad VA, et al. *Langmuir* (2021); 37:6178
- [4] *Physicochemical Characterization, Toxicity and In Vivo Biodistribution Studies of a Discoidal, Lipid-Based Drug Delivery Vehicle: Lipodisq Nanoparticles Containing Doxorubicin.* Torgersen ML, et al. *J. Biomed. Nanotechnol.* (2020); 16:41
- [5] *Effects of charged lipids on the physicochemical and biological properties of lipid–styrene maleic acid copolymer discoidal particles.* Tanaka M, et al. *Biochim. Biophys. Acta. Biomembr.* (2020); 1862:183209
- [6] *From polymer chemistry to structural biology: The development of SMA and related amphipathic polymers for membrane protein extraction and solubilization.* Bada Juarez JF, et al. *Chem. Phys. Lipids.* (2019); 221:167
- [7] *The styrene–maleic acid copolymer: a versatile tool in membrane research.* Dörr JM, et al. *Eur. Biophys. J.* (2016); 45:3
- [8] *Reconstitution of membrane proteins: a GPCR as an example.* Goddard AD, et al. *Methods Enzymol.* (2015); 556:405

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#### Lipodisq™ References

- [9] Nano-size uni-lamellar lipodisq improved in situ auto-phosphorylation analysis of *E. coli* tyrosine kinase using (19)F nuclear magnetic resonance. Li D, et al. *Protein Cell* (2015); 6:229
- [10] Characterizing the structure of lipodisq nanoparticles for membrane protein spectroscopic studies. Zhang R, et al. *Biochim. Biophys. Acta.* (2015); 1848:329
- [11] Advances in the use of nanoscale bilayers to study membrane protein structure and function. Malhotra K and Alder NN. *Biotechnol. Genet. Eng. Rev.* (2014); 30:79
- [12] DEER EPR measurements for membrane protein structures via bifunctional spin labels and lipodisq nanoparticles. Sahu ID, et al. *Biochemistry* (2013); 52:6627
- [13] Detergent-free formation and physicochemical characterization of nanosized lipidpolymer complexes: lipodisq. Orwick MC, et al. *Angew. Chem.* (2012); 51:4653
- [14] Detergent-free incorporation of a seven-transmembrane receptor protein into nanosized bilayer lipodisq particles for functional and biophysical studies. Orwick-Rydmark M, et al. *Nano Lett.* (2012); 12:4687
- [15] In vitro and in vivo evaluation of tumor targeting styrene-maleic acid copolymer-pirarubicin micelles: survival improvement and inhibition of liver metastases. Daruwalla, J, et al. *Cancer Sci.* (2010); 101:1866
- [16] Poly(styrene-alt-maleic anhydride) derivatives as potent anti-HIV microbicide candidates. Fang W, et al. *Bioorg. Med. Chem. Lett.* (2009); 19:1903
- [17] SMA-doxorubicin, a new polymeric micellar drug for effective targeting to solid tumours. Greish K, et al. *J. Control. Release* (2004); 97:219
- [18] Responsive Hydrophobically Associating Polymers: A Review of Structure and Properties. Tonge, SR and Tighe, BJ. *Adv. Drug Deliv. Rev.* (2001); 53:109

Lipodisq™ technology is covered by one or more of the following patents owned by Malvern Cosmeceutics Limited: AU2006253886, CA2611144, CN101184473B, EP1890675, GB2426703, IN261468, JP5142898, US8623414 and WO/2021/005340A1 pending.

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