

**Ivermectin**

## Developer(s)

Merck (known as MSD outside the United States and Canada)

Originator

<https://www.merck.com/stories/mectizan/>

International



Dr. William C. Campbell conducted his co-recipient 2015 Physiology or Medicine Nobel Prize-winning Work at Merck Research Laboratories. He received the prize with Satoshi Omura for the discovery of avermectin which led to Merck's development of ivermectin, to treat river blindness. They share the prize with Youyou Tu for her discoveries concerning a novel therapy against malaria.

Various generic manufacturers

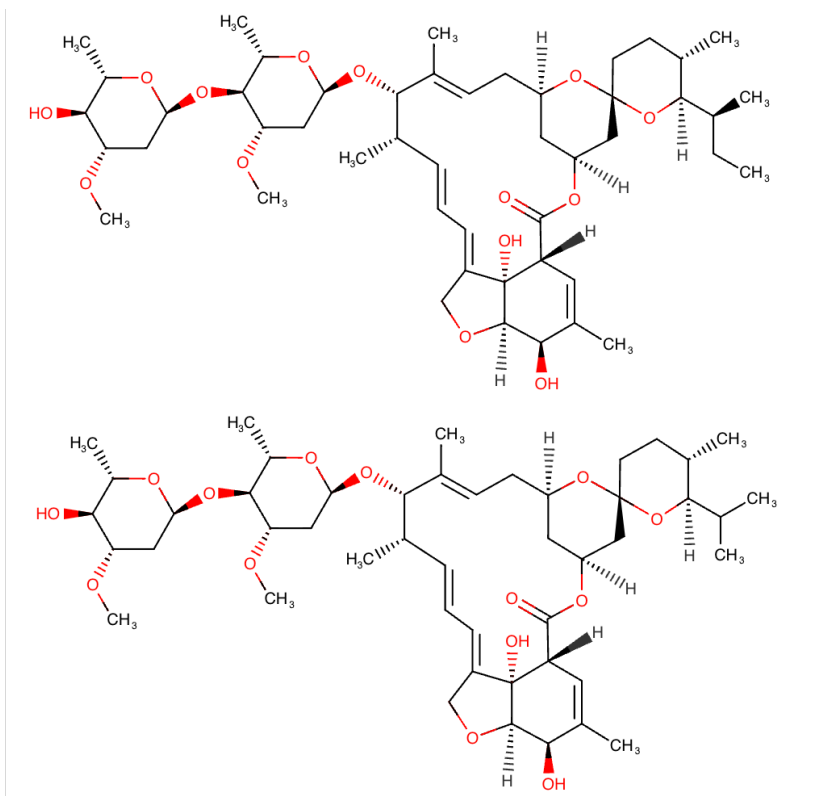
Generic

<https://medex.com.bd/generics/644/ivermectin-tablet>

international

Ivermectin 3mg manufactured buy generic manufactures including: ARROW LAB, BIOGARAN, CRISTERS, EG, EG LABO, PIERRE FABRE, SANDOZ, SIGILLATA, SUBSTIPHARM, TEVA, VIATRIS, ZENTIVA, Taj Pharmaceuticals, Dr. Reddy's labs.

## Drug structure



Ivermectin Chemical Structure

Sourced from Drugbank

# Drug information

## Associated long-acting platforms

Oral solid form, Polymer-based particles

## Administration route

Oral, Subcutaneous

## Therapeutic area(s)

Malaria

COVID 19

Other(s) : "other parasitic infections"

## Use case(s)

Pre-Exposure Prophylaxis (PrEP)

Post-Exposure Prophylaxis (PEP)

Treatment

## Use of drug

### Ease of administration

Administered by a nurse

Administered by a specialty health worker

Self-administered

To be determined

### Frequency of administration

Not provided

## **User acceptance**

Not provided

## **Dosage**

### **Available dose and strength**

Not provided

### **Maximum dose**

Not provided

### **Recommended dosing regimen**

Not provided

### **Additional comments**

Not provided

### **Dosage link(s)**

Not provided

## Drug information

### Drug's link(s)

Not provided

### Generic name

Ivermectin

### Brand name

Not provided

### Compound type

Small molecule

### Summary

Ivermectin is a broad-spectrum anthelmintic that possesses significant potential as a first-in-class endectocide providing vector-based malaria control. Ivermectin functions by binding glutamate-gated chloride channels present in parasital nerve and muscle cells, which results in the elimination of the organism. An extended-release oral ivermectin formulation known as LYN-163 is currently being developed by Lyndra Therapeutics and is undergoing phase I clinical trials. This ultra-long acting, oral drug delivery system is based on their proprietary LYNX™ technology which supports once fortnightly dosing. Other long-acting ivermectin formulations are in the pre-clinical phase and include a polymer-based injectable developed by MedinCell utilising their proprietary BEPO® drug delivery system.

### Approval status

Unknown

### Regulatory authorities

Unknown

## **Delivery device(s)**

Lyndra's proprietary LYNX™ drug delivery platform is a novel approach to oral drug delivery that enables once-a-week or even once-a-month dosing. Key proprietary features include: (1) A flexible core that allows the dosage form to maintain its desired shape in the stomach, preventing premature passage into the small intestine. (2) Linkers connecting dosage form arms to the core. These linkers are designed to soften and disintegrate, allowing the dosage form to safely exit the body. (3) A proprietary coating that makes the capsule easy to swallow and ensures it remains intact in the oesophagus.

# **Scale-up and manufacturing prospects**

## **Scale-up prospects**

Compound is commercially manufactured.

## **Tentative equipment list for manufacturing**

(1) Fermentation & Extraction tanks: Bacterial fermentation vessels to produce avermectin and its subsequent extraction from the fermentation broth. (2) Hydrogenation reactors: Allows the conversion of avermectin to ivermectin by selective hydrogenation. (3) Filtration systems: Removes impurities from the ivermectin solution. (4) Crystallizers: Vessels used to crystallize ivermectin from the solution. (5) Dryers: Required to remove solvent from the crystallized ivermectin. (6) Packaging equipment: Machinery to package the final drug product.

## **Manufacturing**

Avermectin derivatives such as ivermectin are unstable in acidic and alkaline conditions, in addition to being sensitive to strong light. Product formulations containing avermectins usually include antioxidant excipients as they are susceptible to chemical oxidation processes.

## **Specific analytical instrument required for characterization of formulation**

(1) Identification of residual impurities: High-performance liquid chromatography (HPLC), gas chromatography (GC), mass spectrometry (MS). (2) Determine concentration: Ultraviolet-visible spectrophotometry. (3) Elucidate melting point and identify polymorphic forms: Differential scanning calorimetry. (4) Analyse crystal structure and determine polymorphic forms: X-ray powder diffraction (XRPD). (5) Drug solubility: Dissolution testing apparatus.

# Clinical trials

## LYN-163-C-101

### Identifier

ACTRN12621001218886

### Link

<https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12621001218886>

### Phase

Phase I

### Status

Recruiting

### Sponsor

Lyndra® Therapeutics, Inc. (Lyndra)

### More details

Not provided

### Purpose

Evaluate the safety and tolerability of long-acting oral capsules (LYN-163) containing 28mg ivermectin in a drug-releasing formulation.

### Interventions

#### Intervention 1

Drug: LYN-163 LAO capsule without stabilizing ring (dose of 28mg ivermectin)

## **Intervention 2**

Drug: LYN 163 LAO capsule with stabilizing ring (dose of 28 mg ivermectin)

## **Intervention 3**

Drug: LYN 163 LAO capsules with stabilizing ring (dose of 56 mg ivermectin)

## **Countries**

Australia

## **Sites / Institutions**

Not provided

## **Trials dates**

### **Anticipated Start Date**

Not provided

### **Actual Start Date**

2022-05-26

### **Anticipated Date of Last Follow-up**

Not provided

### **Estimated Primary Completion Date**

2023-04-15

### **Estimated Completion Date**

2023-04-15

### **Actual Primary Completion Date**

Not provided

### **Actual Completion Date**

Not provided

## **Studied populations**

### **Age Cohort**

- Adults

### **Genders**

- Male
- Female

### **Accepts pregnant individuals**

No

### **Accepts lactating individuals**

No

### **Accepts healthy individuals**

Yes

## **Comments about the studied populations**

Participants are healthy male and female individuals aged between 18-49 years, with a body weight greater than or equal to 56 kg. Participants are excluded if they have a history of X-ray, computed tomography scan, or angiogram of the abdomen within one year of Screening.

### **Health status**

Negative to : HIV, HBV, HCV, COVID 19

### **Study type**

Interventional (clinical trial)

### **Enrollment**

25

### **Allocation**

Non-randomized

## **Intervention model**

Parallel Assignment

## **Intervention model description**

Not provided

## **Masking**

Open label

## **Masking description**

None (Open label)

## **Frequency of administration**

Other : "Single dose "

## **Studied LA-formulation(s)**

Tablet

## **Studied route(s) of administration**

Oral

## **Use case**

PrEP

## **Key resources**

Not provided

# Excipients

## **Proprietary excipients used**

Not provided

## **Novel excipients or existing excipients at a concentration above Inactive Ingredients Database (IID) for the specified route of administration**

Not provided

## **Residual solvents used**

Not provided

## Patent info

## **Description**

Long-acting injectable ivermectin formulation

## **Brief description**

This invention relates to novel, long-acting injectable formulations. These formulations comprise: (a) a therapeutic agent selected from the group consisting of, e.g., insecticides, acaricides, parasiticides, growth enhancers and oil-soluble NASIDS; (b) hydrogenated castor oil and (c) a hydrophobic carrier comprising: (i) triacetin, benzyl benzoate or ethyl oleate or a combination thereof; and (ii) acylated monoglycerides, propyl dicaprylates/dicaprates or caprylic/capric acid triglycerides or a combination thereof. Also provided herein is a method for the treatment or prevention of various disease states by the parental administration of the invention formulations.

## **Representative patent**

WO1999027906

## **Category**

Formulation

## **Patent holder**

Merck Sharp & Dohme Corp; Merial LLS (acquired by BI)

## **Exclusivity**

Long-acting injectable parasiticide formulation of specific excipients and therapeutic agent such as ivermectin, for various use including the prevention and treatment of parasitic infestation

## **Expiration date**

September 14, 2018

## **Status**

Expired

## **Description**

Ivermectin compound

### **Brief description**

Derivatives of C-076 are described in which the C-076 molecule, as series of macrolides, has a specific unsaturation, at the 22,23-position, catalytically reduced. Further reaction of the reduced C-076 compounds are also possible. The compounds thus produced have profound anthelmintic, insecticidal, ectoparasitocidal and acaracidal activity. Compositions containing the described C-076 derivatives as the active ingredient thereof are also disclosed.

### **Representative patent**

US4199569

## **Category**

Compound

### **Patent holder**

Merck & Co, Inc.

### **Exclusivity**

Not provided

### **Expiration date**

April 22, 1997

## **Status**

Expired

## **Supporting material**

## Publications

Andrew M. Bellinger *et al.* Oral, ultra-long-lasting drug delivery: Application toward malaria elimination goals. *Sci. Transl. Med.* **8**,365ra157-365ra157(2016).DOI:

[10.1126/scitranslmed.aag2374](https://doi.org/10.1126/scitranslmed.aag2374)

Efforts at elimination of scourges, such as malaria, are limited by the logistic challenges of reaching large rural populations and ensuring patient adherence to adequate pharmacologic treatment. We have developed an oral, ultra-long-acting capsule that dissolves in the stomach and deploys a star-shaped dosage form that releases drug while assuming a geometry that prevents passage through the pylorus yet allows passage of food, enabling prolonged gastric residence. This gastric-resident, drug delivery dosage form releases small-molecule drugs for days to weeks and potentially longer. Upon dissolution of the macrostructure, the components can safely pass through the gastrointestinal tract. Clinical, radiographic, and endoscopic evaluation of a swine large-animal model that received these dosage forms showed no evidence of gastrointestinal obstruction or mucosal injury. We generated long-acting formulations for controlled release of ivermectin, a drug that targets malaria-transmitting mosquitoes, in the gastric environment and incorporated these into our dosage form, which then delivered a sustained therapeutic dose of ivermectin for up to 14 days in our swine model. Further, by using mathematical models of malaria transmission that incorporate the lethal effect of ivermectin against malaria-transmitting mosquitoes, we demonstrated that this system will boost the efficacy of mass drug administration toward malaria elimination goals. Encapsulated, gastric-resident dosage forms for ultra-long-acting drug delivery have the potential to revolutionize treatment options for malaria and other diseases that affect large populations around the globe for which treatment adherence is essential for efficacy.

Bellinger AM, Jafari M, Grant TM, Zhang S, Slater HC, Wenger EA, Mo S, Lee YL, Mazdiyasni H, Kogan L, Barman R, Cleveland C, Booth L, Bensel T, Minahan D, Hurowitz HM, Tai T, Daily J, Nikolic B, Wood L, Eckhoff PA, Langer R, Traverso G. Oral, ultra-long-

lasting drug delivery: Application toward malaria elimination goals. *Sci Transl Med*. 2016 Nov 16;8(365):365ra157. DOI: 10.1126/scitranslmed.aag2374. PMID: 27856796; PMCID: PMC5264553.

Efforts at elimination of scourges, such as malaria, are limited by the logistic challenges of reaching large rural populations and ensuring patient adherence to adequate pharmacologic treatment. We have developed an oral, ultra-long-acting capsule that dissolves in the stomach and deploys a star-shaped dosage form that releases drug while assuming a geometry that prevents passage through the pylorus yet allows passage of food, enabling prolonged gastric residence. This gastric-resident, drug delivery dosage form releases small-molecule drugs for days to weeks and potentially longer. Upon dissolution of the macrostructure, the components can safely pass through the gastrointestinal tract. Clinical, radiographic, and endoscopic evaluation of a swine large-animal model that received these dosage forms showed no evidence of gastrointestinal obstruction or mucosal injury. We generated long-acting formulations for controlled release of ivermectin, a drug that targets malaria-transmitting mosquitoes, in the gastric environment and incorporated these into our dosage form, which then delivered a sustained therapeutic dose of ivermectin for up to 14 days in our swine model. Further, by using mathematical models of malaria transmission that incorporate the lethal effect of ivermectin against malaria-transmitting mosquitoes, we demonstrated that this system will boost the efficacy of mass drug administration toward malaria elimination goals. Encapsulated, gastric-resident dosage forms for ultra-long-acting drug delivery have the potential to revolutionize treatment options for malaria and other diseases that affect large populations around the globe for which treatment adherence is essential for efficacy.

Awasthi A, Razzak M, Al-Kassas R, Harvey J, Garg S. An overview on chemical derivatization and stability aspects of selected avermectin derivatives. *Chem Pharm Bull (Tokyo)*. 2012;60(8):931-44. DOI: 10.1248/cpb.c12-00258. PMID: 22863694.

Naturally occurring avermectins (AVMs) and its derivatives are potent endectocide compounds, well-known for their novel mode of action against a broad range of

nematode and anthropod animal parasites. In this review, chemical and pharmaceutical aspects of AVM derivatives are described including stability, synthetic and purification processes, impurities and degradation pathways, and subsequent suggestions are made to improve the chemical stability. It has been found out that unique structure of AVM molecules and presence of labile groups facilitated the derivatization of AVM into various compounds showing strong anthelmintic activity. However, the same unique structure is also responsible for labile nature related to sensitive stability profile of molecules. AVMs are found to be unstable in acidic and alkaline conditions. In addition, these compounds are sensitive to strong light, and subsequently presence of photo-isomer in animals treated topically with AVM product is well known. The pharmacoepial recommendations for addition of antioxidant into drug substance, as well as its products, arises from the fact that AVM are very sensitive to oxidation. Formations of solvates, salts, epoxides, reduction of double bonds and developing liquid formulation around pH 6.2, were some chemical approaches used to retard the degradation in AVM. This coherent review will contribute towards the better understanding of the correlation of chemical processes, stability profile and biological activity; therefore, it will help to design the shelf-life stable formulations containing AVMs.

## **Additional documents**

No documents were uploaded

## **Useful links**

There are no additional links

# Access principles

## Collaborate for development



Consider on a case by case basis, collaborating on developing long acting products with potential significant public health impact, especially for low- and middle-income countries (LMICs), utilising the referred to long-acting technology

Not provided

## Share technical information for match-making assessment



Provide necessary technical information to a potential partner, under confidentiality agreement, to enable preliminary assessment of whether specific medicines of public health importance in LMICs might be compatible with the referred to long-acting technology to achieve a public health benefit

Not provided

## Work with MPP to expand access in LMICs



In the event that a product using the referred to long-acting technology is successfully developed, the technology IP holder(s) will work with the Medicines Patent Pool towards putting in place the most appropriate strategy for timely and affordable access in low and middle-income countries, including through licensing

Not provided

## Comment & Information

Not provided