FONDAZIONE PER LA RICERCA FARMACOLOGICA GIANNI BENZI ONLUS

UNIVERSITÀ DEGLI STUDI DI BARI ALDO MORO

XVI FORESIGHT TRAINING COURSE
Repurposing to cover unmet needs: the current scenario in Europe and the proposed changes to the Pharmaceutical Legislation

Experience and Plan from companies and SMEs Repurposing Colchicine for Heart Disease

Serena Tongiani, Ph.D.
Chief Portfolio Officer, Indena SPA

18 Dec 2023 - Bari, Italy

Indena

Industria Derivati Naturali

OUR MISSION

At Indena we believe that an in-depth knowledge in **active ingredients derived from medicinal plants** and the search for excellence at all times are crucial commitments to serving our customers in pharmaceuticals and health-foods.

Research and production technologies are the main focus of our mission and the way we create a “value difference” for our partners.

At Indena, we have always been inspired by a rigorous scientific approach in our research:

PROCESS RESEARCH
PRODUCT RESEARCH

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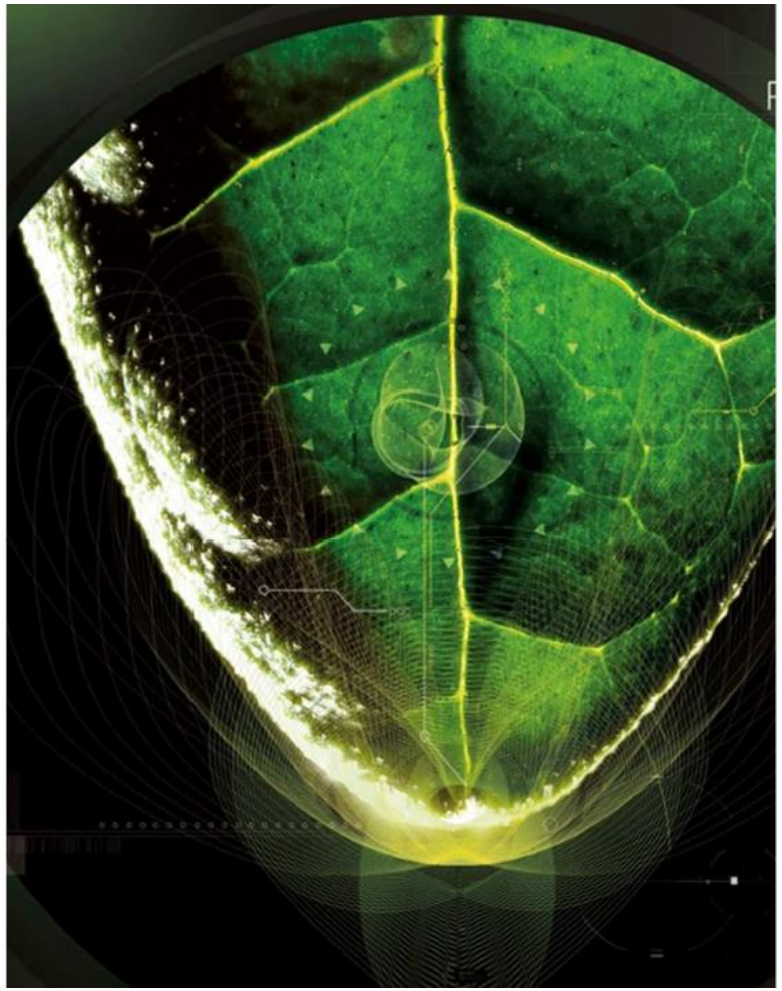
«The Best Chemist is Nature»



PHARMACEUTICALS

Since 1921 we've been taking inspiration from Nature with scientific advancements. Bright minds come together at Indena to support human health toward a new, healthier future. Among our main products:

PACLITAXEL
Taxus media Rehder - Anticancer, Antimitotic

10-DAB III
Taxus baccata L. - Chemical intermediate

THIOCOLCHICOSIDE
Gloriosa superba L. - Muscle relaxant

COLCHICINE
Gloriosa superba L. – Antigout

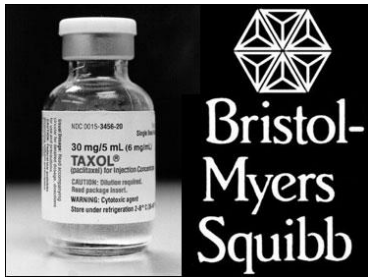
DOCETAXEL
Taxus baccata L. - Anticancer, Antimitotic

MYRTOCYAN®
Vaccinium myrtillus L. - Capillar fragility, Venous insufficiency

ESCIN
Aesculus hippocastanum L. – Antioedema

GINKGO BILOBA
Ginkgo biloba L. - Blood circulation health

CABAZITAXEL
***Taxus baccata* L.** - Anticancer, Antimitotic



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Repositioning: We see the story from the API and Supply Chain

Drug repositioning Strategy advantages:

- reduced number of required clinical trial steps could reduce the time and costs for the medicine to reach market
- **existing pharmaceutical supply chains (including API) could facilitate "formulation and distribution" of the drug**

Many company are looking to reposition drugs when IP on API is expired

- known possibility of combining with other drugs could allow more effective treatment
- the repositioning could facilitate the discovery of "new mechanisms of action for old drugs and new classes of medicines
- the removal of “activation barriers” of early research stages can enable the project to advance rapidly into disease-oriented research

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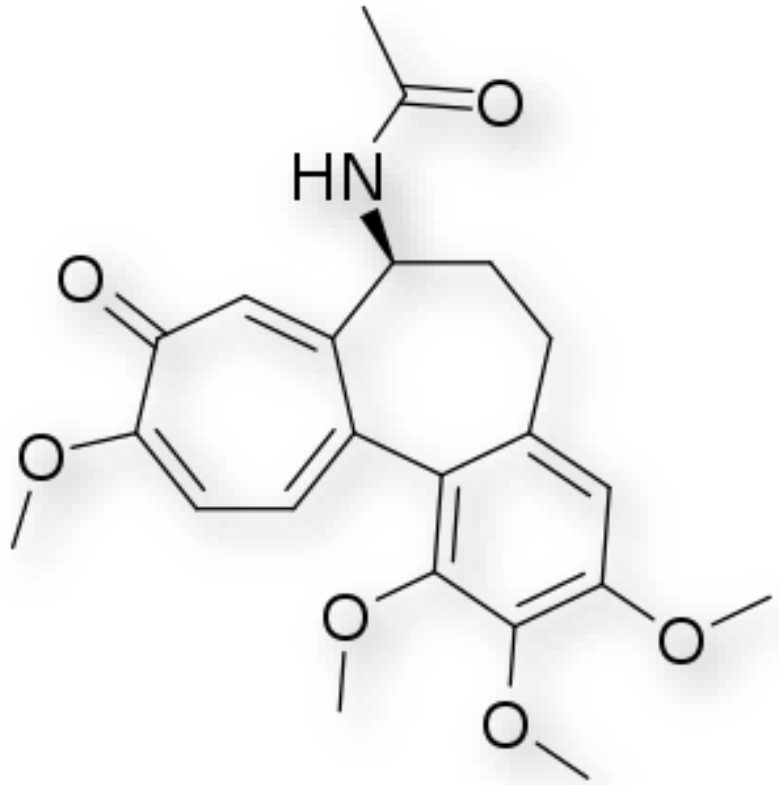
And we follow the repurposing story from API production… some have happy endings other do not …



Colchicine

Gloriosa Superba

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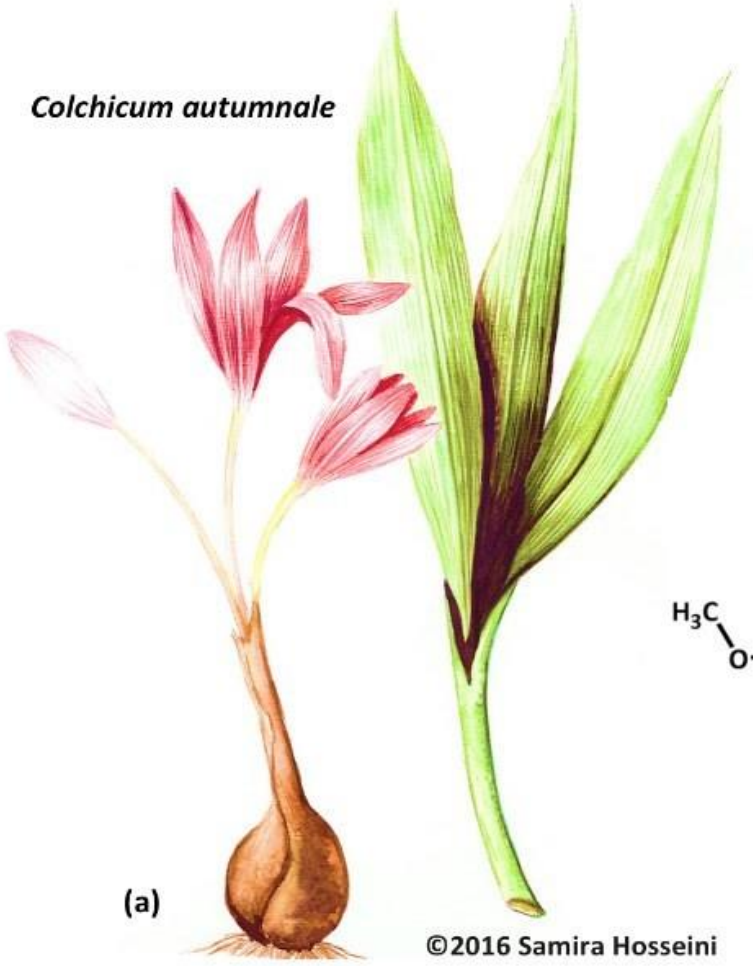
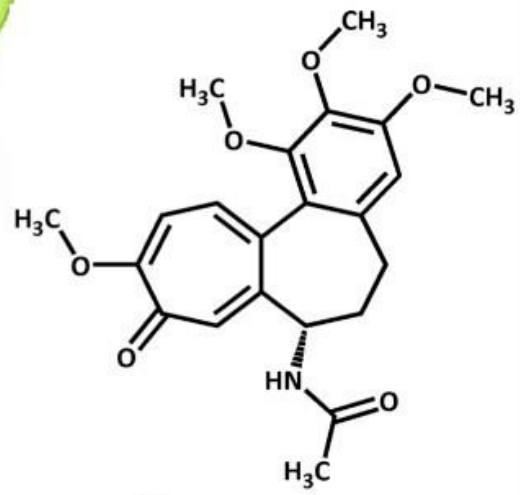
WHATCH OUT!



Colchicine



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Colchicine Therapeutical Indication

Colchicine is indicated in the majority of the Countries for:

1.Gout:

- Colchicine is commonly prescribed to treat acute gout attacks. It helps alleviate pain and inflammation associated with gout by reducing the inflammatory response to uric acid crystals in the joints.

2.Familial Mediterranean Fever (FMF):

- Colchicine is also used as a preventive treatment for FMF, a genetic disorder characterized by recurrent episodes of fever, inflammation, and pain.

3.Pericarditis:

- In some cases, colchicine may be prescribed to manage acute pericarditis, an inflammation of the lining around the heart (the pericardium).

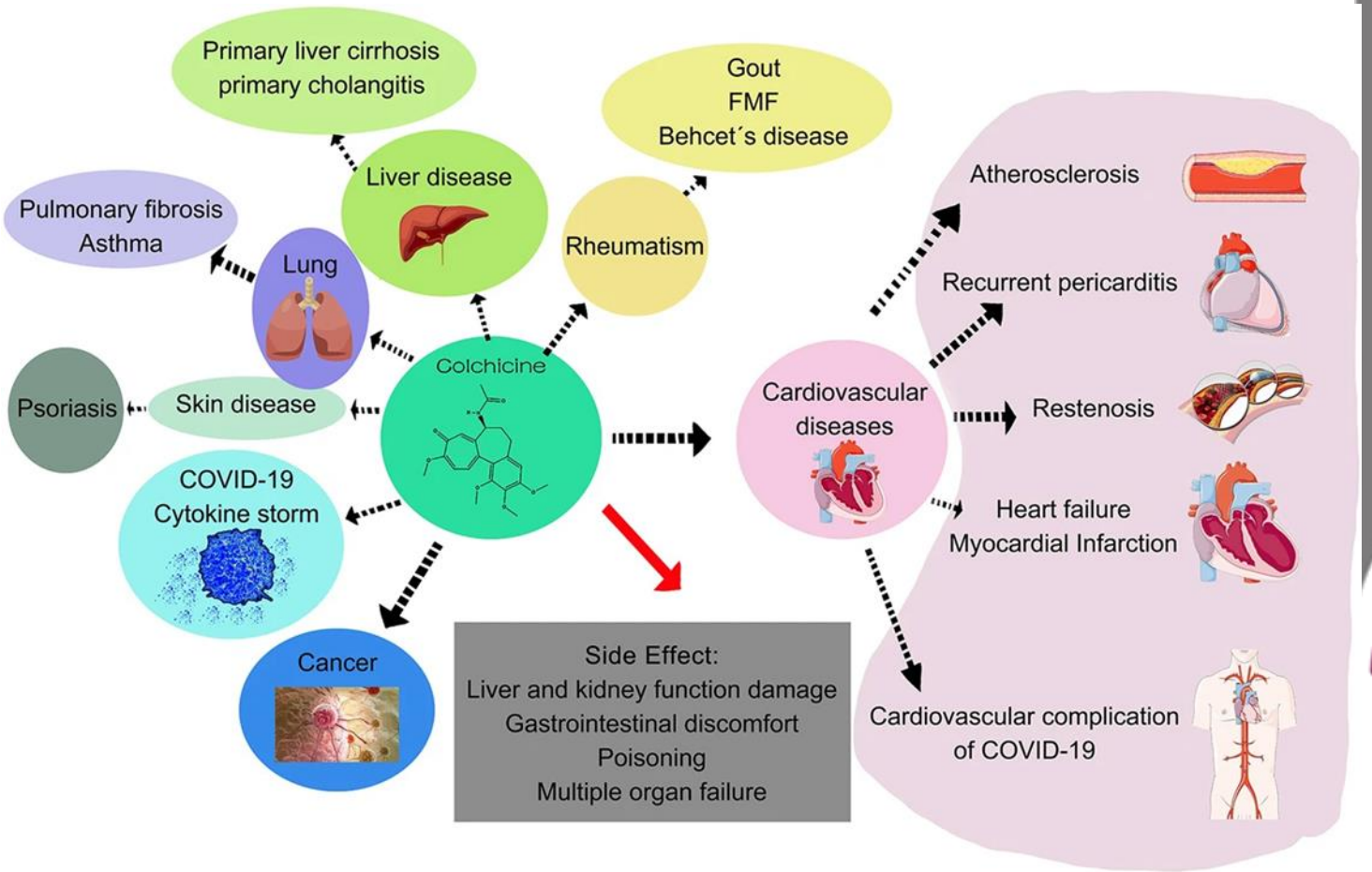
Tablet for Oral use 1mg and (only in few countries) 0.5mg

Colchicine Mechanism of Action repurposing strategy gold standard

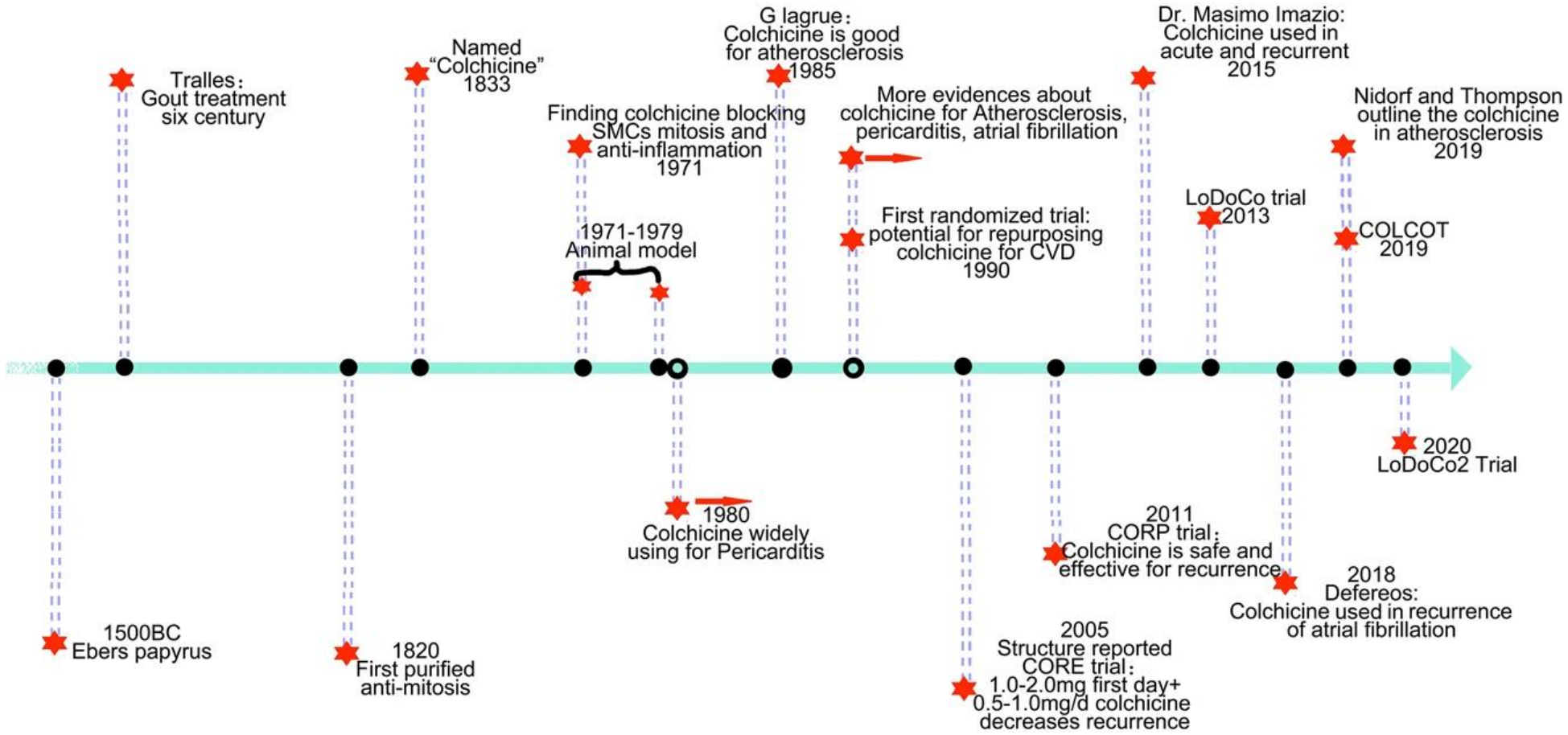
Acts inhibiting the release of chemiotactic factors and glycoproteins

Binds to fibrillary protein and inhibits granulocites migration to joints

Also has amiotic action and increase gut motility



Timeline and milestone of colchicine in medicinal history



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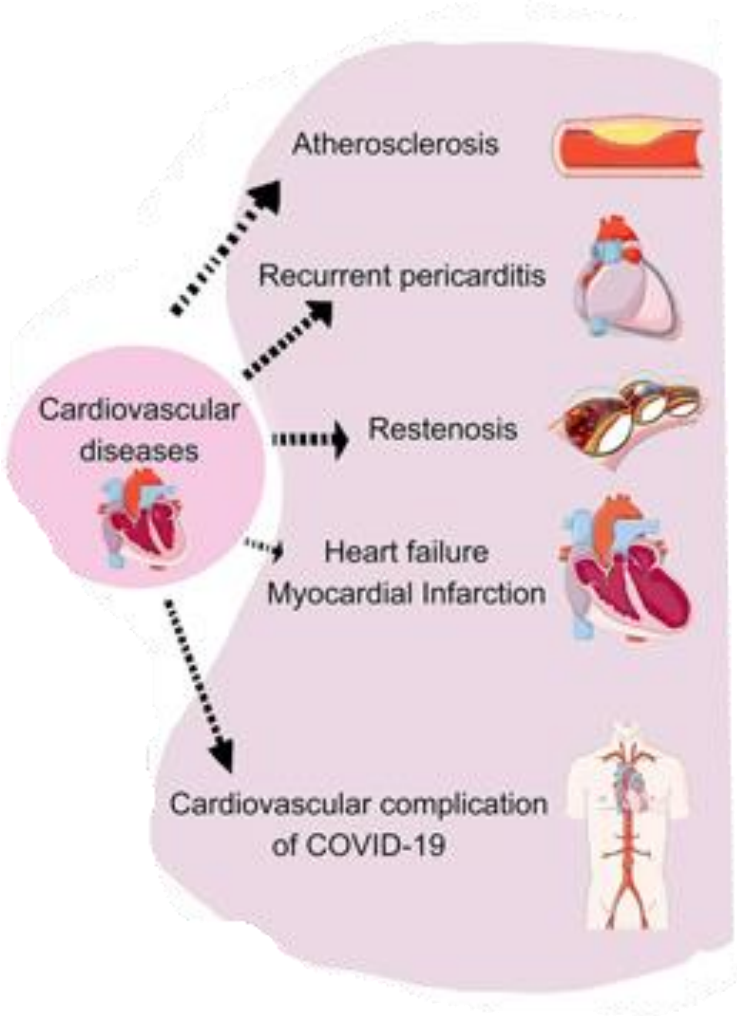
CONCLUSION OF TWO SUCCESSFUL CLINICAL STUDIES ON USE OF COLCHICINE IN CORONARY ARTERY DISEASE



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction

This article was published on November 16, 2019, at NEJM.org.

DOI: 10.1056/NEJMoa1912388

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Tardif at the Montreal Heart Institute, 5000 Belanger St., Montreal, PQ H1T 1C8, Canada, or at jean-claude.tardif@icm-mhi.org.

CONCLUSIONS

Among patients with a recent myocardial infarction, colchicine at a dose of 0.5 mg daily led to a significantly lower risk of ischemic cardiovascular events than placebo. (Funded by the Government of Quebec and others; COLCOT ClinicalTrials.gov number, NCT02551094.)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Colchicine in Patients with Chronic Coronary Disease

This article was published on August 31, 2020, at NEJM.org.

DOI: 10.1056/NEJMoa2021372

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Nidorf at GenesisCare, 3/140 Mounts Bay Rd., Perth 6000, WA, Australia, or at smnidorf@gmail.com; or to Dr. Mosterd at the Department of Cardiology, Meander Medical Center, P.O. Box 1502, 3800 BM Amersfoort, the Netherlands, or at a.mosterd@meandermc.nl.

CONCLUSIONS

In a randomized trial involving patients with chronic coronary disease, the risk of cardiovascular events was significantly lower among those who received 0.5 mg of colchicine once daily than among those who received placebo. (Funded by the National Health Medical Research Council of Australia and others; LoDoCo2 Australian New Zealand Clinical Trials Registry number, ACTRN12614000093684.)

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ESC European Society of Cardiology
European Heart Journal (2021) **42**, 3227–3337
doi:10.1093/eurheartj/ehab484

2021 ESC Guidelines on cardiovascular disease prevention in clinical practice

Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies

With the special contribution of the European Association of Preventive Cardiology (EAPC)

3.2.3.7 Risk estimation and risk factor treatment in patients with established atherosclerotic cardiovascular disease

Occasionally, recurrent CVD risk is very high despite maximum (tolerated) conventional treatments. In such cases, novel but less well-established preventive treatments such as dual antithrombotic pathway inhibition,[83] icosapent ethyl,[84] or anti-inflammatory therapy with colchicine (see *section 4.10*)[85,86] may be considered.

COLCOT STUDY MENTIONED IN THE BRAND NEW ESC GUIDELINES AND MORE TO COME IN 2022 EDITION

4.10. Anti-inflammatory therapy

Recommendation for anti-inflammatory therapy

Recommendation	Class[a]	Level[b]
Low-dose colchicine (0.5 mg *o.d.*) may be considered in secondary prevention of CVD, particularly if other risk factors are insufficiently controlled or if recurrent CVD events occur under optimal therapy.[85,86]	IIb	A

CVD = cardiovascular; *o.d.* = *omni die* (once a day).
[a]Class of recommendation.
[b]Level of evidence.

In 2019, COLCOT (Colchicine Cardiovascular Outcomes Trial) reported a significant reduction (HR 0.77) in CVD outcomes with low-dose colchicine [0.5 mg *o.d.* (once a day)] in patients with a recent AMI. The more recent LoDoCo2 (second low-dose colchicine) trial reinforced these results in patients with chronic CAD (HR 0.69).[85] This study observed a trend towards increased non-CV mortality, which requires further attention.

The use of colchicine in daily practice remains to be established based on further clinical study data and experiences in daily practice. Nonetheless, the encouraging results justify consideration of low-dose colchicine in selected, high-risk patients.

Canada

Health Canada Approves MYINFLA™ (Colchicine 0.5 mg Extended-Release Tablets), a New Repurposed Treatment for Cardiovascular Disease

Français

NEWS PROVIDED BY
Pharmascience Inc. →
Aug 27, 2021, 06:00 ET

Pr myinfla™ ER
colchicine 0.5 mg
extended-release tablets

On Aug 27 2021 the Health Canada, based on COLCOT results, approves the first 0.5 mg colchicine for prevention of atherothrombotic events in CAD patients

MYINFLA™ is indicated for the reduction of atherothrombotic events in adult patients with existing coronary artery disease, in addition to standard therapies, including LDL-C (low-density lipoprotein cholesterol) lowering and antithrombotic drug treatment. It is formulated in a novel, lower-dose, extended-release tablet.

Health Canada's approval of MYINFLA™ was primarily based on the results of the Colchicine Cardiovascular Outcomes Trial (COLCOT) led by Dr. Jean-Claude Tardif from the MHI, in partnership with Pharmascience. As seen in COLCOT, MYINFLA™ significantly reduced the risk of a first ischemic cardiovascular event and the risk of total ischemic cardiovascular events by 23% and 34%, respectively, in addition to standard of care in patients with a recent myocardial infarction (MI). The primary efficacy endpoint was a composite of cardiovascular death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring coronary revascularization. These results were published in the prestigious New England Journal of Medicine (Tardif *et al., N Engl J Med 2019; 381:2497-505*).

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USA

Current USA indication and dosages

COLCRYS (colchicine, USP) tablets, for oral use
Initial U.S. Approval: 1961

---------- **INDICATIONS AND USAGE** ----------

COLCRYS (colchicine, USP) is an alkaloid indicated for:

- Prophylaxis and treatment of gout flares in adults (1.1).
- Familial Mediterranean fever (FMF) in adults and children 4 years or older (1.2).

---------- **DOSAGE AND ADMINISTRATION** ----------

- **Gout Flares:**

  Prophylaxis of Gout Flares: 0.6 mg once or twice daily in adults and adolescents older than 16 years of age (2.1). Maximum dose 1.2 mg/

PROBENECID AND COLCHICINE
(0.5 gm.) (0.5 mg.)

INDICATIONS: For the treatment of chronic gouty arthritis when complicated by frequent, recurrent, acute attacks of gout.

Each Tablet contains:
Probenecid ..... 500 mg.
Colchicine ..... 0.5 mg.

Danbury
COL-PROBENECID TABLETS
Caution: Federal law prohibits dispensing without Prescription.
APPROVED 1000 TABLETS 3 NOV 1978
DANBURY PHARMACAL, INC.
Danbury, Conn. 06810

Usual adult dosage: One tablet daily for one week, then one tablet twice a day.
See enclosed package insert for other information.

Agepha Pharma gets ancient gout remedy colchicine across FDA finish line for heart disease

- **In June 2023, the U.S. FDA approved a low-dose colchicine regimen for the prevention of heart attacks in adult patients with multiple risk factors for cardiovascular disease. As an anti-inflammatory drug, a dose of 0.5mg/d reduces the rates of cardiovascular events by 25% to 30% in patients with coronary atherosclerosis. The drug is most effective in combination therapy with lipid-lowering and other anti-inflammatory medications**

IP protection for the use of Colchicine in CV indication

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DATA Protection and Price

Initial Exclusivities for New Drugs

Exclusivity is a period of time when a brand-name drug is protected from generic drug competition. There are different exclusivities for different situations. Exclusivity is designed to promote a balance between new drug innovation and generic drug competition.

5 years — New Chemical Entity (NCE) Exclusivity

In most cases, a brand-name drug with a new active moiety has a **five-year** exclusivity.

7 years — Orphan Drug Exclusivity (ODE)

A new brand-name drug for a disease or condition that affects fewer than 200,000 people in the United States (or that affects more people but for which the drug company still has no hope of covering the development costs) has a **seven-year** exclusivity.

3 years — New Clinical Investigation Exclusivity

A brand-name drug with an active ingredient that has been approved before may be awarded a **three-year** exclusivity in certain circumstances, such as if a new way of delivering the active ingredient is proposed (for example, a tablet rather than a liquid) or a different disease or condition the drug can treat is identified. To get this approval, the drug company must conduct new clinical studies in humans.

October 2023
a retail price was issue for Lodoco of $**621 for** a 30-day supply -- nearly $21/pill.

Additional Exclusivities May Be Eligible

Pediatric: A brand-name drug for which the sponsor has done pediatric studies (in response to a written request from FDA) may be eligible for a **six-month** exclusivity, which is added on to any other exclusivities or patents for that drug.

Antibiotic: Certain new antibiotic drugs for specific infectious diseases may be eligible for a **five-year** exclusivity, which is added on to any other exclusivities for that drug.

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What about old Europe?

Medical Opinion is in favor:

Based on its long-term safety and effectiveness, low-dose colchicine is poised to be repurposed as a new cornerstone therapy for the secondary prevention of coronary disease. It is already included in the guidelines in many countries, including Europe, Canada, South America, and Taiwan.

- Why company do not see the opportunity?
- Is the off label use enough for the patient needs?

References

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Montreal Heart Institute, Montreal, Quebec H1T 1C8, Canada; Faculty of Medicine, Université de Montréal, Montreal, Quebec H3C 3J7, Canada

Drug repositioning: a brief overview Jean-Pierre Jourdana,b , Ronan Bureaua , Christophe Rochaisa and Patrick Dallemagnea a UNICAEN, Centre d'Etudes et de Recherche sur le Medicament de Normandie (CERMN), Normandie Univ., and b Pharmacy Department, CHRU de Caen, Caen, Fran

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