19th Expert Committee on the Selection and Use of Essential Medicines

Application for Colchicine

November 30th, 2012

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1. **Summary statement of the proposal for inclusion**

Colchicine was first registered in 1947 in France and is currently indicated for the treatment of rheumatic and non-rheumatic diseases:

- Acute gout attack
- Prevention of gout attack when starting a uric acid lowering therapy
- Other microcrystalline arthritis (in some countries)
- Familial Mediterranean Fever
- Behcet disease (in some countries)

During its meeting in 2005, the Expert Committee on the Selection and Use of Essential Medicines, recommended that colchicine be deleted from the Model List because of its unfavourable benefit-risk ratio when compared with non-steroidal anti-inflammatory drugs (NSAIDs) for most people with gout.

At that time and for the treatment of acute gout attacks in some countries (USA in particular), colchicine was used at high doses, up to 6mg on the first day with a high incidence of gastro-intestinal adverse effects such as diarrhoea.

Over the recent years, new clinical data confirmed that lower doses were more effective with an efficacy level similar to that of high doses and a safety profile dramatically improved yielding to a more favorable benefit/risk ratio.

In addition, recent epidemiological data highlighted the frequency of comorbidities such as hypertension, coronary artery disease, chronic kidney disease, hyperlipidemia and diabetes mellitus, in patients with gout. These comorbidities and their respective treatment have to be considered when choosing a first line therapy. Depending on the kind of comorbidity, colchicine appears more appropriate than NSAIDs in some patients.

As a consequence, colchicine was reintroduced or maintained (depending on the territory) in international guidelines or recommendations, as one of the appropriate primary option for the management of gout attack.

In non-rheumatic disease, colchicine is the only worldwide licensed drug with a major favorable benefit-risk ratio for the treatment of Familial Mediterranean Fever (FMF), the most frequent auto-inflammatory disease which affects children and adults.

Thus, our proposal for inclusion of colchicine in the Model list is mainly based on the:

- revised benefit-risk ratio of colchicine in the management of patients with gout attack
- the essential place of the colchicine in the management of patients with FMF
2. Name of the focal point in WHO submitting or supporting the application (where relevant)

Colchicine is again one of the primary options for the management of patient with gout.

Colchicine is an essential drug in the management of patients with Familial Mediterranean Fever (FMF) for prophylaxis of attacks and prevention of amyloidosis.

3. Name of the organization(s) consulted and/or supporting the application

The application is based on published international consensus or recommendations.

4. International Nonproprietary Name (INN, generic name) of the medicine

Colchicine

5. Formulation proposed for inclusion; including adult and paediatric (if appropriate)

Tablet from 0.5 mg to 1mg strength

6. International availability - sources, if possible manufacturers and trade names

Colchicine is available in most countries under various trade names (See Index Nominum – MICROMEDEX® 2.0 dated October 2012 in annex I)
Laboratoires MAYOLY SPINDLER has registered Colchicine Opocalcium® or Colchicine Capel® in 25 countries listed in Annex II.
Colchicine Opocalcium® or Colchicine Capel® is manufactured in France by SANOFI WINTHROP INDUSTRIE. Colchicine is controlled according to analytical procedures described in the European Pharmacopoeia monograph N°0758.

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Individual medicine

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

Gout:

Gout is the most common inflammatory arthritis and may be associated with impaired quality of life. Gout prevalence estimate vary between 1% and 2% in developed countries [26]
An accurate and detailed summary of gout’s prevalence in different countries and regions of the world was reported by (28). Its prevalence varies widely from country to country. Regional differences may reflect environmental, dietary, and genetic influences.

Gout is a debilitating illness in which recurrent episodes of pain and joint inflammation are caused by the formation of crystals within the joint space and deposition of crystals in soft tissue. If untreated, these disorders can lead to joint destruction and renal damage.

Gout and hyperuricemia are associated with numerous comorbidities particularly: hypertension, coronary artery disease, hyperlipidemia, metabolic syndrome, chronic kidney disease, obesity and diabetes mellitus. Therefore, considerations and precautions are necessary when treating gouty arthritis in these patients (19 12).

Familial Mediterranean Fever (FMF)

FMF is the most common auto-inflammatory disease. It has traditionally been regarded as being inherited in an autosomal recessive manner, although some recent articles have reported a significant number of patients with only one mutation. FMF is divided in two main phenotypes. Type 1 is characterized by recurrent short episodes of inflammation and serositis including fever, peritonitis, synovitis, pleuritis and rarely pericarditis and meningitis. The symptoms vary from one patient to another. Amyloidosis which can lead to renal failure is the most severe complication of FMF. Type 2 is characterized by amyloidosis as the first clinical manifestation of the disease in otherwise asymptomatic individuals (27). Mean age at clinical disease onset is 4 years (before 20 years in 90% of cases and before 1 year in 10%) (14).

FMF generally affects eastern Mediterranean people, mainly non Ashkenazi Jews, Arabs, Armenians and Turks with a prevalence of 1/200 à 1/1000 (31-5). However possibly due to extensive population movements, it has been reported throughout the world including Japan (23-20).

9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostics, treatment or monitoring facilities and skills)

Acute Gout Attack

Besides clinical expertise acquired over decades, current recommendations related to the use of colchicine are based on 2 randomized controlled studies:

- Forty three patients with acute gout attack were randomized in a placebo controlled trial to receive either oral colchicine (n=22) or a matching placebo (n=21). The initial dose of colchicine was 1mg, followed by 0.5mg every two hours until complete response or toxicity (nausea, vomiting, or diarrhea) occurred. Patients entered the study 38 hours (mean
duration) from the onset of symptoms and were assessed every six hours for 48 hours. Using a 50% decrease in baseline measures as the criterion of improvement, a significantly greater proportion of patient taking colchicine improved with respect to pain and clinical score and did so earlier than the placebo group (clinical score at 12h, 24, 36h and 48 hours was: 5%, 23%, 50% and 64% versus 0%, 0%, 5% and 23% respectively and pain score at 12h, 24, 36h and 48 hour was: 23%, 41%, 73% and 73% versus 9%, 9%, 32% and 36% respectively). In all patients taking colchicine, diarrhea and/or vomiting occurred at a median time of 24 hours or after a mean dose of 6.7mg colchicine (1).

This dose of colchicines which was considered in some countries as the conventional dosing is no longer appropriate or indicated (9).

- In a multicenter, randomized, double-blind, controlled, parallel-group study, Terkeltaub and colleagues (2010) compared self administered low dose colchicine with high dose colchicine or placebo for the treatment of acute gout attack, using the US formulation of colchicine (0.6mg tablet).

Among 575 patients with a known history of gout, 185 developed an acute gout flare and were randomly assigned, within the 12 hours of the onset of symptoms, to one of the three treatment groups: (1) low-dose colchicine (n = 74), 1.2 mg initially, followed by 0.6 mg in 1 hour (1.8 mg total over 1 hour), followed by placebo doses every hour for five hours; (2) high-dose colchicine (N = 52) with 1.2 mg initially, followed by 0.6 mg every hour for 6 hours (4.8 mg total); or (3) placebo (N = 58).

The primary outcome was the proportion of patients who had a ≥ 50% reduction of pain (on a 0-10 Likert pain scale) within 24 hours of the first dose of medication.

37.8% of patients in the low-dose treatment group, 32.7% in the high-dose group and 15.5% in the placebo group met the primary endpoint (p=0.005 and p=0.034, respectively, versus placebo).

Rescue therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) could be administered by a study physician if intolerable pain continued after at least 1 dose of study drug but those patients were considered non responders. Overall, rescue medications (NSAIDs) were taken within the first 24 hours by 31.1% of patients in the low-dose group (p=0.027 versus placebo), 34.6% in the high-dose group (p=0.103 versus placebo), and 50.0% in the placebo group.

Adverse events, primarily diarrhoea, occurred significantly more frequently in the high-dose group and there were no significant differences in adverse events between the low-dose and placebo groups.

The authors concluded that low-dose colchicine (1.8 mg total over 1 hour) yielded to efficacy comparable with that of high-dose colchicine (4.8 mg total over 6 hours) when given in early onset gout flare and with a safety profile similar to that of placebo (30).

Because of these latest study, the lower dose regimen of colchicine for the treatment of gout attack, was included in all international recommendations.

In European recommendations for the management of gout attack, the nonsteroidal anti-inflammatory drugs (NSAIDs) and/or oral colchicine are the recommended first-line treatments for acute gout.
For colchicine, EULAR experts state that low dose (for example 0.5mg three times daily) may be sufficient for some patients with acute gout (35).

According to the British Society for Rheumatology, colchicine should be used at the maximum dose of 2mg per day and is designated as an effective alternative to NSAIDs (10).

In the American guidelines, NSAIDs or oral colchicine are the recommended first-line treatments for acute gout, as well as systemic corticosteroids. A combination of these medications can be used for severe or unresponsive cases. The ACR experts recommend colchicine for gout attacks when the onset is no greater than 36 hours prior to treatment initiation with a loading dose of 1.2mg of colchicine followed by 0.6mg one hour later, and then 0.6mg once or twice daily (unless dose adjustment is required) 12 hours later, until the gout attack resolves (9-13).

In addition, recommended doses of colchicine has been reduced by 50%, in patients with risk of toxicity such as elderly people (>75 years of age), patients with renal or hepatic impairment, concomitant treatment that might impair renal/hepatic function or induce bone marrow/muscular toxicity or might interact with colchicine (P-glycoprotein or strong CYP3A4 inhibitors).

**Prevention of acute gout attacks**

Two randomized placebo-controlled trials of colchicine for the prevention of gout attacks are published.

In the first one (3), 43 patients with crystal-proven gouty arthritis who had criteria for initiating allopurinol were randomized to receive colchicine 0.6 mg twice daily or placebo (n=22). Patients with renal insufficiency received 0.6 mg colchicine once daily. Subjects initiated allopurinol therapy at a dose of 100 mg daily and increased allopurinol dosing by 100 mg/d increments until serum uric acid was less than 6.5 mg/dL. Patients were evaluated at 3 and 6 months for gout flares and for adverse events.

Patients treated with colchicine experienced fewer acute gout flares in the 0-3 month time period and in the 3-6 month time period as compared to placebo-treated patients (p <0.05 for both comparisons). Overall, fewer gout flares were observed in the colchicine group than in the placebo group (12 flares versus 65). A smaller proportion of patients in the colchicine arm experienced flares (33%) than in the placebo group (77%) and more patients had multiple flares in the placebo group (63%) than in the colchicine group (14%).

The second study (25), was a 6- month, randomized, double-blind, placebo-controlled study of colchicine for the prevention of gout flares in patients with gout starting on ULT with probenecid. A total of 52 patients were randomized to colchicine 0.5 mg/probenecid or placebo/probenecid, 3 times daily. To assess the effect of colchicine on preventing gout flares the number of gout flares per month was analyzed: patients in the colchicine-probenecid group had a lower rate of gout flares per month than patients receiving placebo (0.19 versus 0.48, p< 0.05).
According to American and European guidelines prophylaxis against gout attack during the first 6 to 12 months of ULT (uric acid lowering therapy), can be achieved by colchicine 1 mg per day or an NSAID with gastroprotection, if indicated. The choice of the drug should include an analysis of patient comorbidities and concomitant treatment. When necessary the daily dose of colchicine should be reduced accordingly and patients should be monitored closely for possible adverse effects of colchicine.

Conversely to colchicine, NSAIDs are not currently approved for prophylaxis by the FDA (9).

**Familial Mediterranean Fever (FMF)**

The daily administration of colchicine is the standard therapy for prophylaxis of attacks and amyloid deposition in FMF patients.

**Prophylaxis of attacks**

The discovery of colchicine as an effective drug for FMF attacks came from open labeled trials and was reported in the early 1970s (6-36).

In 3 independent placebo controlled trials on small FMF patients groups, colchicine led to a significant reduction in the number of attacks in adults (7-36-4).

In children, evidence for the effectiveness of colchicine came from open labeled studies (18-37-30). Long term application of colchicine led to a complete remission in approximately two third and a partial remission in approximately one third of the patients with FMF. A minority (5%) did not respond to this treatment.

From the national registry (2838 adults and children patients, mean age 23 ± 13.33, range: 2-87 years), the Turkish FMF Study group reports that all but 2.4% of patients had been prescribed colchicine with 80% reporting regular use, 17% irregular use and 0.6% during attacks only. Among these patients, 51.2% had complete response, 46% had occasional attacks and 2.8% were not responsive.

In FMF patients, non response to colchicine has been related to the 3435C genotype of the transporter molecule ABCB1 or P-glycoproteine (29).

These findings point out that colchicine prevents FMF attacks in more than 90% of patients.

**Prophylaxis of Amyloidosis**

During an observation period of 4 to 11 years, 30% of adult patients without treatment developed long term proteinuria whereas only 0.4% of patients taking colchicine showed kidney involvement. None of the patients with persisting attacks despite colchicine treatment developed long term proteinuria (37).

Among 809 pediatric patients on colchicine, no manifestations of amyloidosis were observed (37-18). In a cohort of 704 children, one patient developed end-stage renal disease, most likely because of poor compliance (24). In the Turkish FMF registry, 2.3%
developed amyloidosis and were not compliant with respect to regular colchicine intake \(^{31}\).

These findings point out that regular intake of colchicine prevents amyloidosis.

**Treatment of amyloidosis**

In a subgroup of pediatric and adult patients, it was demonstrated that colchicine may stabilize or even improve proteinuria secondary to amyloidosis \(^{37-18-17}\). Several reports have shown a stabilization and/or improvement of renal function after colchicine introduction in children and adults with already established nephrotic syndrome resulting from amyloidosis but no improvement was documented in patients with end-stage renal disease \(^{17}\).

**Colchicine dosage in patient with FMF**

Majeed et al reported that 0.5mg/day of colchicine in children < 5 years of age, 1mg/day in children between 5 and 10 years of age and 1.5mg/day in children > 10 years of age was successful in the majority of children \(^{23}\). In a large pediatric cohort the final colchicine dosage at the end of the observation period was 1mg/day in 40%, 1.5mg/day in 25% and 2mg/day in 35% of the patients. Patients in whom 2mg/day was not sufficient to control attacks did not benefit from an additional increase of dosage. It is important to note that the final dosage was assigned irrespective of age and body size. The dose was only adjusted for symptom control \(^{29}\). The colchicine dose was also proposed to be established according to body weight: 0.03mg/kg/day with a maximum of 3mg daily. The aim of the therapy being not only to prevent attacks but also to control subclinical inflammation in the free intervals, that is achieved by maintaining seroamyloid A protein value below 10mg/l \(^{5}\).

Colchicine is usually administered in one or two divided doses daily. In an open randomized trial on 39 patients, Kosan and Ozkan have shown that total dose of colchicine up to 2mg/day may be taken on a once a day basis \(^{15}\).

In large long term cohort studies including adults and children, the dose was adjusted for symptom control. When using that approach, development of proteinuria was rare (0.4%) or not observed at all \(^{18-36}\).

In the high risk group of patients with kidney transplantation for secondary amyloidosis, the development of amyloid deposition was significantly associated with low colchicine doses \(\leq 1\) mg/day \(^{21}\).

In children with amyloid nephropathy, high daily doses \((1.5 – 2\) mg/day) lead to improvement of impaired renal function in approximately two thirds of patients \(^{22}\).

No dose ranging studies have been performed. However, colchicine dose of 0.5 to 2mg /day appears sufficient for the prevention of attacks and amyloid deposition in most patients.
**FMF and pregnancy**

Colchicine did not adversely affect pregnancies in a group of 36 women with FMF who had taken colchicine for 3 to 12 years. The authors of a long term study of 45 FMF patients who had taken colchicine for many years concluded that at therapeutic doses, the drug is safe to use during pregnancy.\(^{(2)}\)

In a study of 116 women Rabinovitch et al showed that chronic colchicine treatment for many years prior to pregnancy and continuous treatment during conception and pregnancy did not increase abnormalities in the newborns or cause any growth or developmental disturbances in the children. The same author also reported, 430 amniocentesis in FMF women with no cases of trisomy 21 or 23. Other reported links with birth defects are isolated and inconclusive.

**FMF and breast feeding**

Colchicine is distributed into breast milk. One study calculated the dose per kg ingested by the infant during the 8 hours following maternal dosing to be 10% of the dose per kg taken by the mother.\(^{(8-2)}\)

Recommendations have been made to wait for 8 to 12 hours after a dose before breast feeding to minimize infant exposure of the infant; However the American Academy of Pediatrics considered its use to be usually compatible with breast feeding because no adverse event have been reported.

**In 2007, the interdisciplinary group of German and Turkish physicians made a review on the efficacy and adverse events of colchicine therapy in children and adolescents with FMF.**

The analysis was intended to:

- Grade evidence of colchicine therapy
- Increase the awareness of colchicine use and improve the adherence to this medication
- Answer questions about the practical application
- Identify important unsolved issues,

The objective was to elaborate a consensus statement.

The analysis was based on caregivers meeting held in Dusseldorf and in Berlin (2004), extensive literature search using PubMed’s Medline with the key words “familial Mediterranean fever” and “age 0-18 years” and published results from colchicines treatment trials. The consensus was approved by the pharmacotherapy working group of the Scientific Society of Pediatric Rheumatologists in Germany and Austria.\(^{(11)}\)

- **Indication and efficacy in FMF**

  1. The continuous use of colchicine for prophylaxis of attacks and prevention of amyloidosis is recommended for children with FMF
  2. Colchicine should be introduced in children with FMF as soon as the diagnosis has been established and continued for life
3. Colchicine is recommended for the treatment of amyloidosis. Dosage should be adjusted for age and renal function

- **Application and dose finding**
  1. A starting dose of ≤ 0.5mg/day (for children < 5 years of age), 1mg/day (for children 5-10 years of age), or 1.5mg/day (for children > 10 years of age) should be administered orally. Colchicine dosage should be increased in a stepwise fashion (eg, 0.25mg/step) up to a maximum of 2mg/day to control disease in patients who do not clinically respond to the standard dosage.
  2. In high risk patients (eg, after kidney transplantation, patients with amyloidosis), higher colchicine doses (up to 2mg/day) should be applied independent of the dose needed for control of clinical symptoms.
  3. Monitoring has to be careful in the presence of impaired renal function or liver function. For patients with severe renal failure (GFR < 10mL/min), the dosage should be reduced by 50% (eg ≤ 1mg/day).

These data are in accordance with recent review from Shohat in 2011 and public assessment report from EMA (27, 21).

10. **Summary of comparative effectiveness in a variety of clinical settings:**

- Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)
- Summary of available data* (appraisal of quality, outcome measures, summary of results)
- Summary of available estimates of comparative effectiveness

**Acute Gout attack**

Current international recommendations and guidelines for the management of gout attack propose Colchicine (low dose), NSAIDs (high dose) or corticosteroids as first line treatment. However few RCT were performed and none of them compared the proposed options. Therefore, no direct comparison between NSAID and colchicine is available (32).

**Prevention of acute gout attacks**

For prophylaxis of acute gout flares which occur with urate lowering therapy (ULT) initiation, the European recommendations and American guidelines recommend oral colchicine or low-dose NSAIDs.

No direct comparative data are available
Conversely to colchicine, NSAIDs are not currently approved for prophylaxis in several countries including the USA (9).

**Familial Mediterranean Fever (FMF)**

Except versus placebo, no comparative data are available. However colchicine use in the management of FMF in adults and children is well documented. Colchicine is an essential first line therapy for patients with FMF in the prophylaxis of attacks and of amyloidosis (23).
11. Summary of comparative evidence on safety*:
- Estimate of total patient exposure to date
- Description of adverse effects/reactions
- Identification of variation in safety due to health systems and patient factors
- Summary of comparative safety against comparators

Based on gout prevalence, we can estimate that several millions of patients are exposed to colchicine each year. The estimate number of patients with FMF is much lower, around 150,000 worldwide but in most of them colchicine is administered for life. Colchicine has a narrow therapeutic margin.

Before colchicine treatment initiation, special attention has to be attributed to comorbidities and concomitant treatment in order to adapt the dose according to the patient conditions while avoiding possible drug interactions.

In long term treatment clinical workup with respect to possible adverse effects including laboratory examination should be performed every 6 months.

Description of adverse effects/reactions

The most frequent adverse effects are digestive disorders, particularly diarrhoea. In such case, dose reduction is recommended.

The side effects are listed below by organ class and frequency. Frequencies are defined as very frequent (≥1/10), frequent (≥ 1/100 and < 1/10), infrequent (≥ 1/1000 and < 1/100), rare (≥ 1/10000 and <1/1000) and very rare (<1/10000) including isolated cases. The frequent and very frequent effects have generally been described in clinical trials. The rare and very rare undesirable effects are generally notified spontaneously once the product is on the market.

Gastro-intestinal disorders
Frequent: diarrhoea, nausea, vomiting. These are the first signs of an overdose. These effects are usually mild or moderate and reversible upon lowering the dose.

Hepatobiliary disorders
Rare: increase in transaminases

Musculo-skeletal and connective tissue disorders
Infrequent: neuromyopathic disorders, reversible upon cessation of treatment.
Very rare: rhabdomyolysis.

Blood and lymphatic system disorders
Infrequent: leucopenia, neutropenia, thrombopenia.
Very rare: pancytopoenia due to medullary toxicity has been reported in patients at risk of colchicine overdose and/or patients undergoing treatment likely to induce medullary toxicity

Skin and subcutaneous tissues disorders
Rare: Urticaria and morbilliform eruptions
Very rare: alopecia, reversible upon cessation of treatment

Reproductive system and breast disorders
Exceptional: azoospermia, reversible upon cessation of treatment.

In the absence of comparative clinical studies, no comparative safety data are available.

12. Summary of available data on comparative cost** and cost-effectiveness within the pharmacological class or therapeutic group:
   • range of costs of the proposed medicine
   • comparative cost-effectiveness presented as range of cost per routine outcome (e.g. cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, or, if possible and relevant, cost per quality-adjusted life year gained)

In most countries (except in the USA), the public price of colchicine appears to be between 0.11 and 0.13 USD for 1mg tablet.
There is no available comparative cost effectiveness study except one performed in the USA (33) but it appears inconsistent to extrapolate the results.

13. Summary of regulatory status of the medicine (in country of origin, and in other countries as well)

Colchicine was first registered in France in 1947 and is now available in most countries


Colchicine which is marketed in France and in the countries listed in annex II is controlled according to analytical procedures described in the European Pharmacopoeia monograph N°0758. Its specification are also in accordance with those described in the European Pharmacopoeia monograph N°0758.

15. Proposed (new/adapted) text for the WHO Model Formulary

Colchicine is the oldest available treatment for gout. Colchicine has a narrow therapeutic margin with a dose dependant toxicity. Recent clinical study has shown the efficacy of colchicine at low dose especially when administered early after the symptoms onset with a dramatically improved safety profile. These new data account
for the inclusion of colchicine as a possible first line therapy for acute gout attack in the current international recommendations. In addition, recent epidemiological data highlighted the frequency of comorbidities such as hypertension, coronary artery disease, chronic kidney disease, hyperlipidemia and diabetes mellitus, in patients with gout. These comorbidities and their respective treatment have to be considered when choosing a first line therapy. In this respect, colchicine appears to be a useful alternative of NSAIDs, especially for patients with hypertension, cardiac insufficiency or patients receiving anticoagulants.

Colchicine is also an appropriate treatment for the prevention of gout flares when initiating a uric acid lowering therapy. In that indication the duration of treatment is of at least 3 to 6 months and here again, colchicine is an alternative to the use of NSAIDs which are not registered for that indication in many countries.

In non rheumatic disease, colchicine is the only worldwide licensed drug with a major favorable benefit-risk ratio for the prophylaxis of attacks and amyloidosis in children and adults with Familial Mediterranean Fever (FMF).

16. References : annex 3
Annex 1

Index Nominum
Index Nominum Abbreviations Key

Foreign Names
L: Colchicum
D: Colchicin
F: Colchicine

ATC
M04AC01

Therapeutic Category
Treatment of gout

Chemical Name
\( \text{C}_{22}\text{H}_{25}\text{N}_{2}\text{O}_{10}\text{S}_2 \)

CAS Number
0000064-86-8

Chemical Formula
C_{22}H_{25}N_{2}O_{10}S_{2}

Mol. wt.
398.452

Structure of Colchicine

Synonyms
OS: Colchicine [IAN, DCF]
P.H. Colchicin [Ph. Eur. 1]
P.H. Colchicine [BP 2011, JP XV, Ph. Eur. 7, Ph. Int. 4, USP 34]
P.H. Colchicine orsabilisée [Ph. Franç. X]
P.H. Colchicinum [Ph. Eur. 7, Ph. Int. 4]
Artico® MediLab, FR
Arterscal® [† Allopurinol] Sedrop-Caution, AR
Articherine® ECU, EC
Aspen Colchicine Aspen Pharmacare, ZA
Cocine® Praxa-lab, TH
Cocine® Borya's Chemical, MM
Cocine® Hua Shin, TW
Cotrocine® Astar, TW
Index Nominum: International Drug Directory
Edited by the Swiss Pharmaceutical Society
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15
# ANNEX 2

Worldwide registration status for Colchicine® Oopalcium

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Annex 3

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