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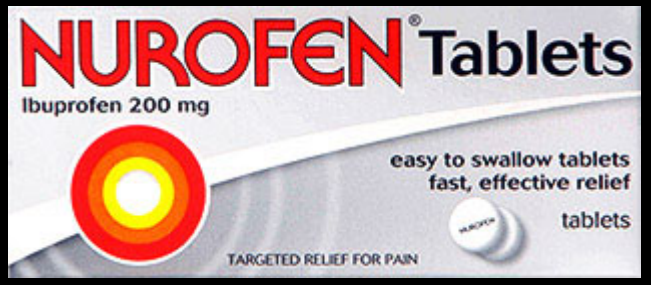
Drug Development
Ibuprofen

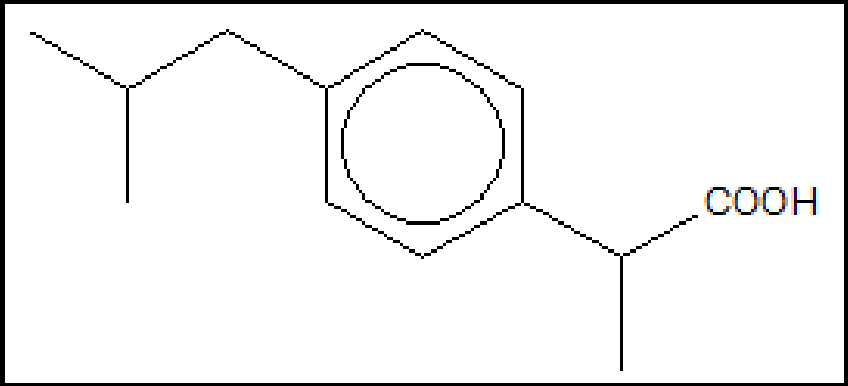
Introduction

- an **anti-inflammatory** drug
- **NSAID**
- possesses **pain-relieving** and **fever-reducing** properties
- particular use in **pain relief from arthritis**

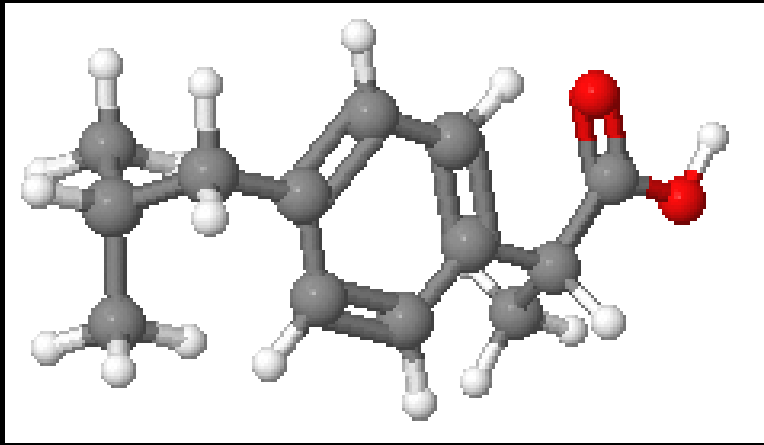


Introduction (cont'd)

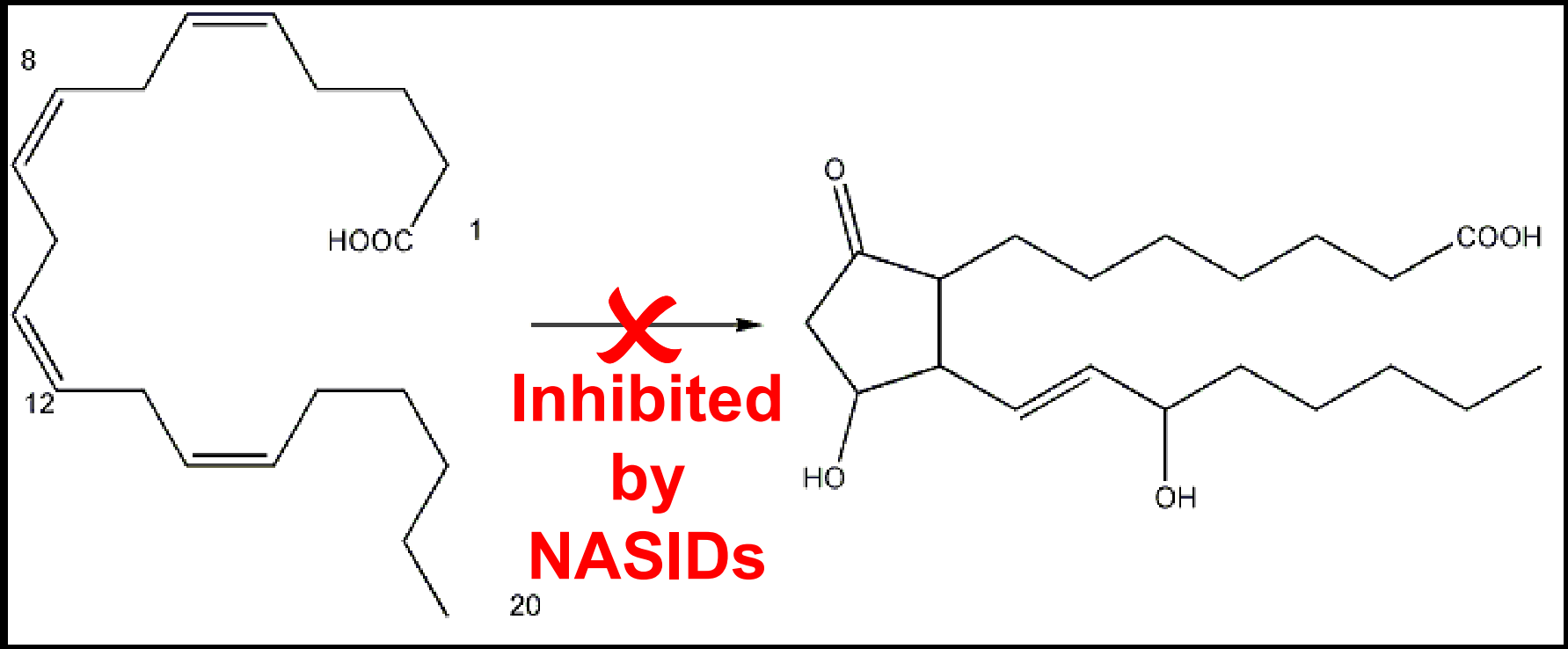
- 2D Structure of Ibuprofen



- 3D Structure of Ibuprofen



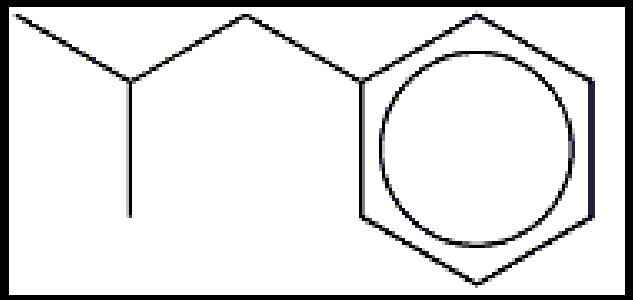
Principle



Arachidonic acid **Prostaglandin**

Lead compound discovery

- developed and discovered as a drug by the Boots Company.



- **2-methylpropylbenzene**

Timeline

1955

- **The discovery was made.**
  - anti-inflammatory drugs
  - simple screening test for new chemical compounds

1956

- **Research was started.**

Aspirin and **phenylbutazone** were available.
Objective:
1.To develop a drug to treat **rheumatoid arthritis** (inflamed joints)
2.To have a superior profile both in terms of **potency** and **toxicity** to these two drugs.

Timeline (cont'd)

1958

- compound code named BTS 8402 is given a clinical trial (i.e. a trial on patients).
- **no better than aspirin.**

1961

- A **patent** is filed for the compound **2-(4-isobutylphenyl) propanoic acid**
- later called **ibuprofen**.

1964

- **further development**

⋮

Timeline (cont'd)

1966

- Northern General Hospital in Edinburgh
- **anti-inflammatory effect** in patients

1969

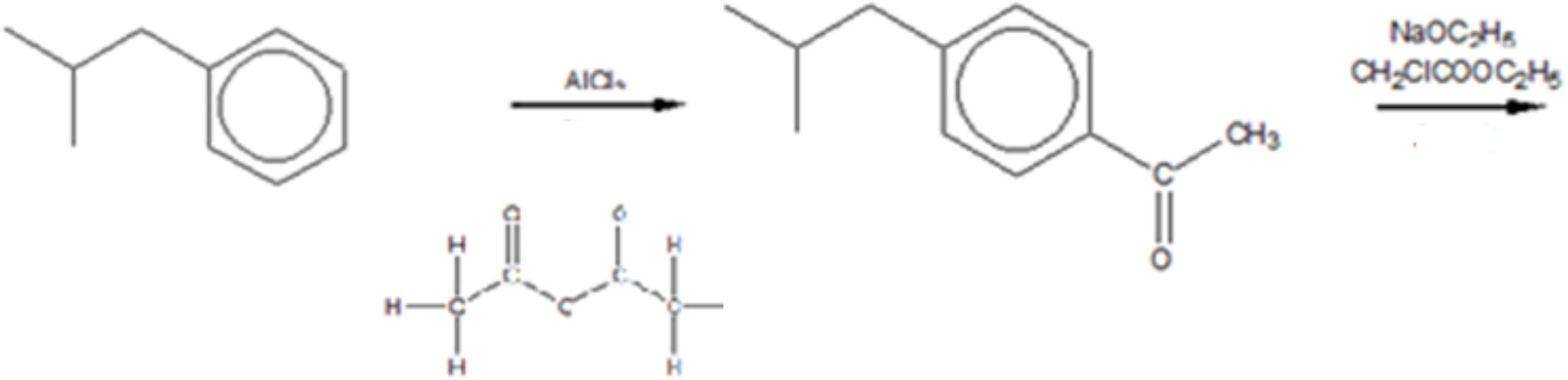
- Clinical trials of Ibuprofen are launched in the UK on prescription only.

1983

- **available** without prescription.

Organic synthesis

- **A)** The **original** Boots synthesis of ibuprofen

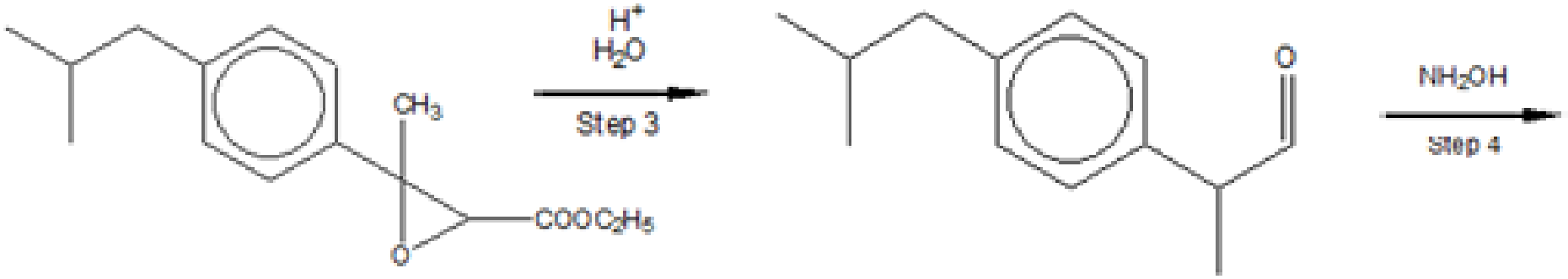


Step1
Friedel-Crafts acetylation
of 2-methylpropylbenzene

Step2
Reaction with ethyl chloroacetate (**Darzens reaction**) gave the α , β -epoxy ester

Organic synthesis(cont'd)

- **A)** The **original** Boots synthesis of ibuprofen

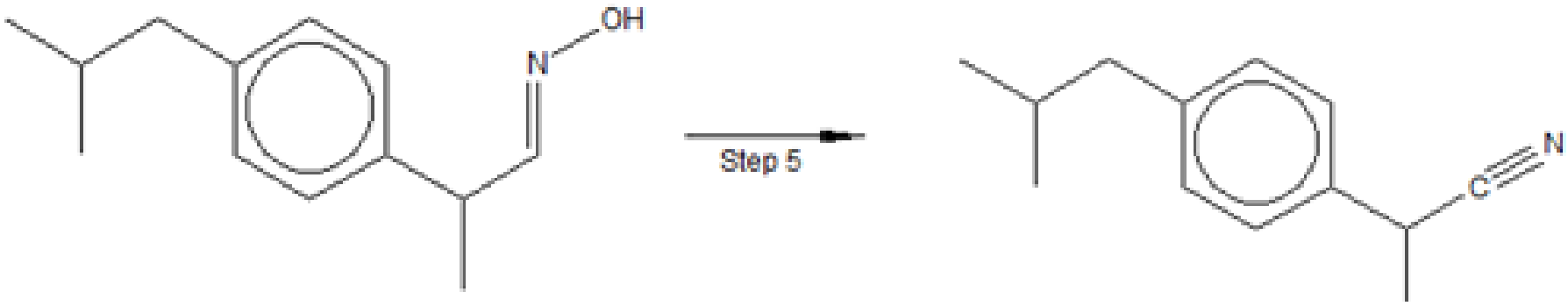


Step3
The α,β-epoxy ester was **decarboxylated and hydrolyzed** to the aldehyde.

Step4
Reaction with hydroxylamine gave the oxime

Organic synthesis(cont'd)

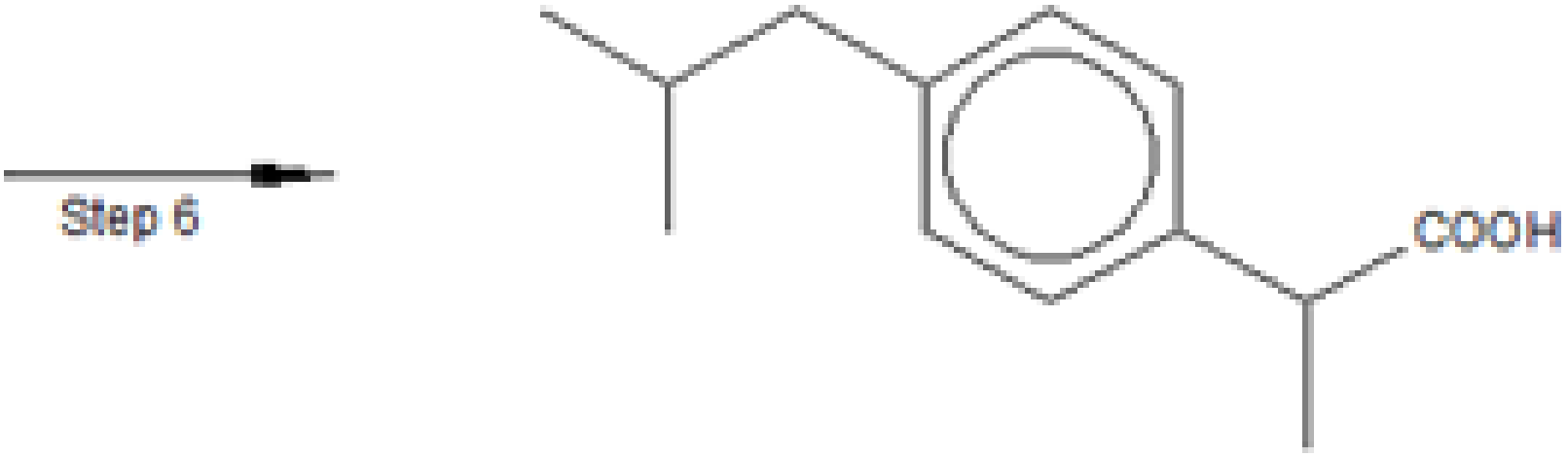
- **A)** The **original** Boots synthesis of ibuprofen



Step5
Then convert to the nitrile

Organic synthesis(cont'd)

- **A)** The **original** Boots synthesis of ibuprofen

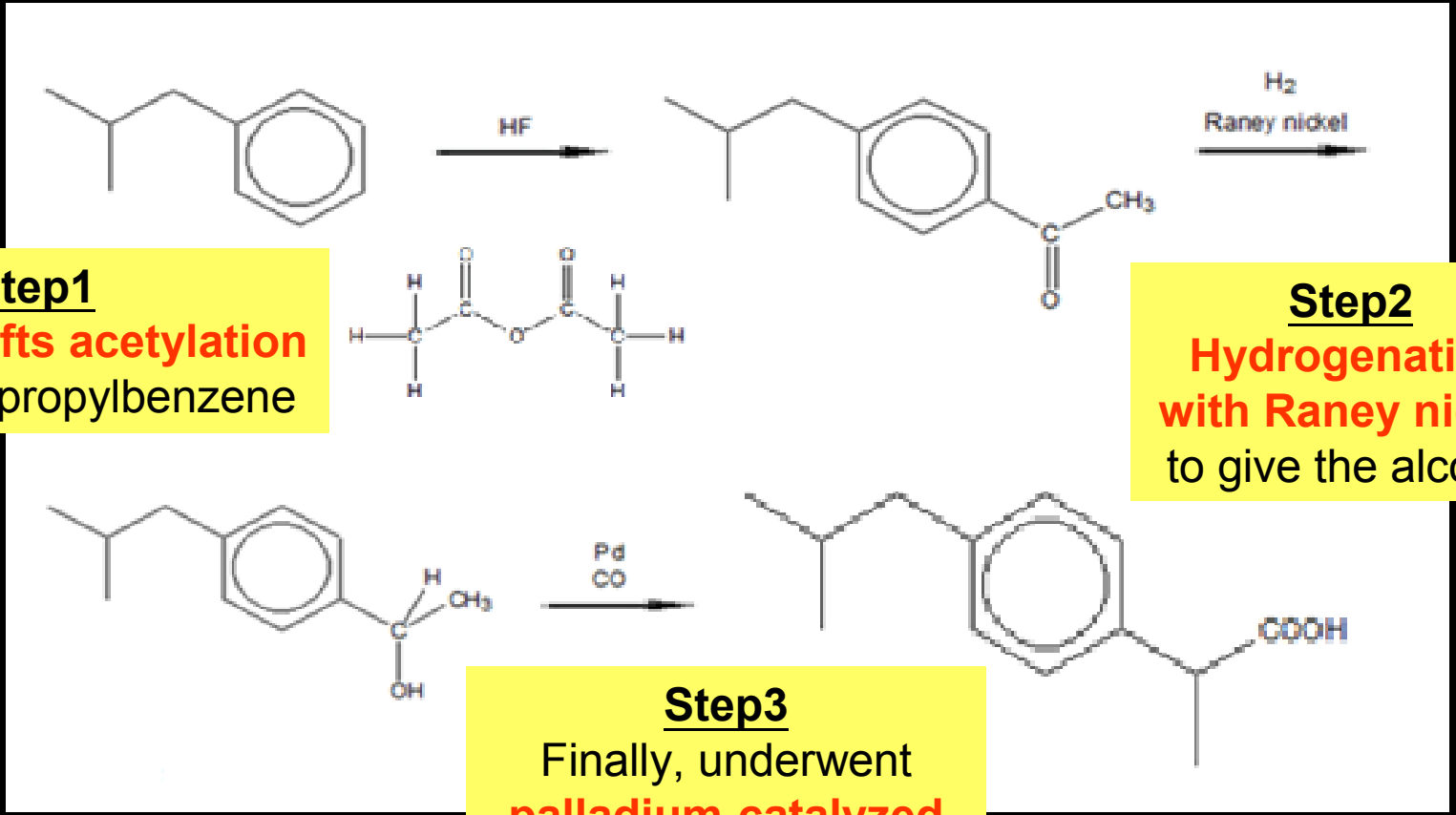


Step6

Finally, **hydrolyze** to the **desired acid(Ibuprofen)**

Organic synthesis(cont'd)

- **B) The advanced 'green' synthesis of ibuprofen**



Step1
Friedel-Crafts acetylation
of 2-methylpropylbenzene

Step2
Hydrogenation with Raney nickel
to give the alcohol

Step3
Finally, underwent
palladium-catalyzed carbonylation

Formulation Development

- the dose of ibuprofen contained in a normal strength tablet is 200 mg (0.2 g)

Formulation Development

Component	Function	Location
Ibuprofen	Active ingredient	Core
Croscarmellose sodium	Disintegrant	Core
Stearic acid	Lubricant	Core
Sodium laurylsulfate	Lubricant	Core
Sodium citrate	Buffering agent	Core
Colloidal anhydrous silica	Anticaking agent	Core
Carmellose sodium	Coating agent	Coat
Carnuba wax powder	Coating agent	Coat
Calcium sulfate dihydrate	Diluent	Coat
Acacia spray dried	Binding agent	Coat
Sucrose	Binding agent	Coat
Titanium dioxide	Pigment	Coat
Purified water	Diluent	Coat

Safety Test

(I)Pre-clinical testing

- Experiment is carried out with cats and rats.

Findings

- **no effect on the cardiovascular system**
- did **not affect the arterial pressure, frequency and strength of cardiac contractions**

Safety Test (cont'd)

(I)Pre-clinical testing

- Examinations of the EEG of cats and rabbits

Findings

- **no departures from the normal whatsoever following administration of the drug**
- **no effect on the spasmogenic effects of**

Safety Test (cont'd)

(II) Human trials

- has undergone extensive clinical trials

Findings:

- **possess high therapeutic activity**
- **improvement in the general condition**
- **reduction in joint pain, morning stiffness, swelling of the joints, etc.**

Approval for marketing

- approved by the FDA in 1974
- approved for sale in the US and other states and its treatment considered effective

Approval for marketing (cont'd)

- **relieve pains of bones and muscles**
- as a **painkiller for inflammation**
- recommended dose is 600-1200 mg daily

In acute conditions

- **increase the daily dose to 1600 mg**

****great care in patients suffering from bronchial asthma**

END