Application for the Inclusion of Theophylline in the WHO Model List of Essential Medicines

SUBMITTED BY:

Chronic Respiratory Disease And Arthritis

Management of Noncommunicable Disease

World Health Organization
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1. **Summary statement of the proposal for inclusion, change or deletion**

Theophylline is proposed to be retained in the WHO Model list of essential medicines for “25. Medicines Action on the respiratory tract” “antiasthmatic and medicines for chronic obstructive pulmonary disease.” Following summary of reports on theophylline shows theophylline is an effective drug with bronchodilating and anti-inflammatory effects and can be used alone or in combination in asthma and COPD. Its safety has been verified. Theophylline is the only oral agent among the essential drugs in asthma and COPD. Current international and national guidelines for asthma and COPD have recommended sustained release theophylline for long-term control of these diseases.

2. **Name of the focal point in WHO submitting or supporting the application**

Dr. Nikolai Khaltaev

Team Leader

Chronic Respiratory Disease and Arthritis Management of Noncommunicable Diseases

World Health Organization

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

GINA (Global Initiative for Asthma)

GOLD (Global Initiative for Chronic Obstructive Lung Disease)

JSA (Japanese Society of Allergology)

JSPA (Japanese Society of Pediatric Allergy)

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

Theophylline

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

Listing is requested on the Model List of Essential Medicines as an individual medicine.
6. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

6.1 epidemiological information on disease burden

GINA (Global Initiative for Asthma)

- Asthma is one of most common chronic disease worldwide, imposing a substantial social burden on both children and adults.
- Asthma occurs in all countries regardless of the level of development but varies greatly between populations, even within countries. There is evidence that over the last 20 years its prevalence has considerably increased, especially among children.
- Strategies to improve asthma control can lead to socioeconomic gains in terms of improved school attendance, fewer absences from work, and, by implication, a smaller burden on families.
- Data on asthma incidence, severity, hospitalization, and mortality are needed for all countries to assist in more effective health planning.
- Developed economies might expect 1 to 2 percent of total health care expenditures to be spent on asthma. Developing economies are likely to face an increased demand for health care expenditures related to asthma.
- Poorly controlled asthma is expensive to manage. Investment in preventive medication is likely to yield cost saving in emergency care for acute exacerbations.

Prevalence of Asthma

CHILDREN

The prevalence of asthma symptoms in children varies from 0 to 30 percent in different populations. Figure 2-1 shows illustrative (not comprehensive) data on the prevalence of current asthma, diagnosed asthma, recent wheeze (symptoms in the last 12 months), airway hyperresponsiveness, and atopy in children. There are many data available for Australia and England, but fewer data for other countries other than those derived from questions on wheeze in the ISAAC study. There are large difference in asthma prevalence among different populations, with the highest prevalence found in Australia, New Zealand, and England. Data are insufficient to determine whether the differences between populations are the consequence of responses to the environment, to industrialization, or to different allergen loads. Although there is some evidence that asthma is less prevalent in
children with high levels of parasitic infections, there have been no systematic studies relating parasitic infections to asthma where there has been adjustment for other environmental factors.

Figure 2-2, from the ISAAC study, shows the prevalence of wheezing in the last 12 months—documented by written questionnaires—among children 13 to 14 years old in a number of populations. The data show a wide range in the prevalence of wheezing in different populations (consistent with the data in Figure 2-1), but few conclusions can be drawn about the risk factors for wheezing in children from these data.

Figure 2-3 shows changes in the prevalence of asthma symptoms in children, young adults, and adults over time. Populations were studied with the same methods on two occasions at least 9 years apart. In all cases an increase in prevalence was documented.

This trend reflects a true increase in asthma prevalence, but is also affected by a recent tendency to label all episodes of wheezing as asthma. Thus, questionnaire estimates may not be regarded as reliable measures of the true change in the prevalence of asthma over time. The reasons for the increase in the prevalence of asthma in children are poorly understood, but are discussed in the chapter on the risk factors.
Adults

Data on prevalence of asthma in adults are more controversial. As can be seen in Figure 2-3, there has been some increase in asthma in adults, but the increase in not as striking as that in children. Figure 2-4 shows data from the adult population in the ECRHS in which airway hyperresponsiveness was measured. However, in many of these studies, the relationship between symptoms and airway hyperresponsiveness has not been reported so it is difficult to define clinically relevant asthma, especially as there was no video questionnaire to document the prevalence of wheezing in the last year that was likely to be due to asthma.

There are few data on asthma in older adults. Although some studies have demonstrated that asthma prevalence among the elderly is equal to that asthma in the elderly in underdiagnosed. Diagnosis of asthma in older adults is often confounded by similar symptoms from cardiac failure and chronic obstructive pulmonary disease,
and normal age-related changes in respiratory function. It is also more difficult because lung function testing is limited in this age group and elderly group are less likely to complain about asthma symptoms and have poorer perceptions of shortness of breath than younger patients.

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Theophylline is a bronchodilator that may have extrapulmonary effects, including anti-inflammatory effects. The bronchodilator effect of theophylline may be related to phosphodiesterase inhibition and is seen at high concentrations (>10mg/l), whereas the anti-inflammatory effect is due to an unknown mechanism and may occur at lower concentrations (5-10 mg/l). At low doses theophylline has some minor influence on chronic airway inflammation in asthma. Most studies show little or no effect on airway
hyperresponsiveness.

Sustained-release theophylline and aminophylline can be used as controller medication in asthma. Many clinical studies have shown that long-term treatment with sustained-release theophylline is effective in controlling asthma symptoms and improving lung function. When given as a sustained-release preparation, it has a long duration of action and is thus useful in the control of nocturnal symptoms that persist despite the regular treatment with anti-inflammatory therapy. Theophylline is also useful as an additional bronchodilator in patients with severe asthma. Now that theophylline at low doses has been shown to be effective in asthma control in both adults and children, it may be used in patients with milder disease and as an add-on therapy to low or high doses of inhaled glucocorticosteroids when further asthma control is needed. As add-on therapy, theophylline is less effective than long-acting β2-agonists. It is, however, a less expensive option.

Due to the risk of adverse effects, and the difficulty of monitoring therapy, theophylline is regarded in some countries as a therapy that should be reserved for use after inhaled glucocorticosteroids and inhaled β2-agonists fail to achieve therapeutic goals. In other countries, theophylline is recommended earlier in the course of daily long-term therapy because it is a bronchodilator useful for the control of asthma, especially of nocturnal asthma symptoms, and it is inexpensive.
7. **Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities and skills)**

**WHO Formulation**

**Theophylline and Aminophylline**

Aminophylline is a representative xanthine bronchodilator. Various drugs including theophylline can serve as alternatives

*Tablets*, theophylline 100 mg

*Modified-release tablets*, theophylline 200 mg, 300 mg

*Injection* (Solution for injection), aminophylline 25 mg/ml, 10-ml ampoule

**Uses:**
- chronic asthma including nocturnal asthma; acute severe asthma

**Contraindications:**
- porphyria; known hypersensitivity to ethylenediamine (for aminophylline)

**Precautions:**
- cardiac disease, hypertension, hyperthyroidism, peptic ulcer, epilepsy, hepatic impairment (Appendix 5), pregnancy (Appendix 2), breastfeeding (Appendix 3), elderly, fever; smokers may require larger or more frequent doses; **interactions**: Appendix 1

**Dosage:**

**Chronic asthma,** *by mouth* (as tablets), **ADULT** and **CHILD** over 12 years, 100–200 mg 3–4 times daily after food; *by mouth* (as modified-release tablets) **ADULT** 300–450 mg every 12 hours

**Nocturnal asthma,** *by mouth* (as modified-release tablets), **ADULT** total daily requirement as single evening dose

**Note.** Plasma theophylline concentration for optimum response 10–20 mg/litre (55–110 micromol/litre); narrow margin between therapeutic and toxic dose; see notes above; a range of 5–15 mg/litre (27.5–82.5 micromol/litre) may be effective and associated with fewer adverse effects

**Acute severe asthma** (*not* previously treated with theophylline), *by slow intravenous injection* (over at least 20 minutes), **ADULT** and **CHILD** 5 mg/kg; maintenance, *by intravenous infusion*, **ADULT** 500 micrograms/kg/hour; **CHILD** 6 months–9 years, 1 mg/kg/hour, 10–16 years, 800 micrograms/kg/hour, adjusted according to plasma-theophylline concentration

**Note.** Patients taking oral theophylline (or aminophylline) should not normally receive intravenous aminophylline unless plasma-theophylline concentration is available to guide dosage

**Adverse effects:**
- nausea and other gastrointestinal disturbances, restlessness, anxiety, tremor, palpitations, headache, insomnia, dizziness; convulsions, arrhythmias and hypotension—especially if
given by rapid injection; urticaria, erythema and exfoliative dermatitis—resulting from hypersensitivity to ethylenediamine component of aminophylline

**US Pharmacopoeia**

Theophylline Tablets, Capuseles

Usual adult dose

Bronchodilator,

Loading dose-

For patients not currently receiving theophylline preparations – Oral, the equivalent of 5 mg of anhydrous theophylline per kg of lean (ideal) body weight as a single dose to provide an average peak serum concentration of 10 mcg per mL (55 micromoles per L), range 5 to 15 mcg per mL (27.5 to 82.5 micromoles per L).

For patients currently receiving theophylline preparations – Obtaining a serum theophylline concentration prior to administering a partial loading dose is recommended. Once the theophylline concentration is known, the loading dose for theophylline is based on the principle that each 0.5 mg of theophylline per kg of lean (ideal) body weight will result in a 1 mcg per mL increase in serum theophylline concentration.

Maintenance-

Oral, the equivalent of anhydrous theophylline, initially 300 mg per day. After three days, the dosage may be increased, if tolerated, to 400 mg per day. After three more days, the dosage may be increased, if tolerated, to 600 mg per day without measurement of serum concentration.

The total daily adult dose is administered in three or four divided doses given about six to eight hours apart. Patients with risk factors for impaired theophylline clearance may require a dosing interval of every twelve hours. Young adult smokers and patients with more rapid metabolism may require a dosing interval of every six hours.

Note: if the 600-mg-per-day dose is to be maintained or exceeded, monitoring of serum theophylline concentration and patient response is recommended to achieve the optimal therapeutic theophylline dosage and minimize the risk of toxicity.
Usual pediatric dose

Bronchodilator-

Loading dose-

For patients not currently receiving theophylline preparations – Infants and children up to 16 years of age: Oral, the equivalent of 5mg of anhydrous theophylline per kg of lean (ideal) body weight as a single dose to provide an average peak serum concentration of 10 mcg per mL (55 micromoles per L), range 5 to 15 mcg per mL (27.5 to 82.5 micromoles per L).

For patients currently receiving theophylline preparations – Obtaining a serum theophylline concentration prior to administering a partial loading dose is recommended. Once the theophylline concentration is known, the loading dose for theophylline is based on the principle that each 0.5 mg of theophylline per kg of lean (ideal) body weight will result in a 1 mcg per mL increase in serum theophylline concentration.

Maintenance-

Children 1 year of age and older, weighting less than 45 kg — Oral, the equivalent of anhydrous theophylline, 12 to 14 mg per kg of body weight, up to a maximum of 300 mg, per day in divided doses. The dosage may be increased, if tolerated, after three days to 16 mg per kg of body weight, up to a maximum of 400 mg per day. After three more days, if tolerated, the dosage may be increased to 20 mg per kg of body weight up to a maximum 600 mg, per day. The total daily dose is administered in four to six divided doses given every four to six hours.

Note: if the 600-mg-per-day dose is to be maintained or exceeded, monitoring of serum theophylline concentration and patient response is recommended to achieve the optimal therapeutic theophylline dosage and minimize the risk of toxicity.

Theophylline Extended-release Tablets

Usual adult dose

Bronchodilator — Oral, the equivalent of anhydrous theophylline, initially, 300 mg per day. If tolerated, the dosage may be increased after three days, to 400 mg per day. After three more days, the dosage may be increased, if tolerated, to 600 mg per day without measurement of serum concentration. One-half the daily theophylline dose may be given at twelve hour intervals. However certain patients metabolize theophylline more
rapidly, especially the young and those that smoke, and may require dosing at eight hour intervals.

Note: If the 600-mg-per-day dose is to be maintained or exceeded, monitoring of serum theophylline concentration and patient response is recommended to achieve the optimal therapeutic theophylline dosage and minimize the risk of toxicity.

Usual pediatric dose

Bronchodilator— Children 1 year of age and older, weighing less than 45kg: Oral, the equivalent of anhydrous theophylline, 12 to 14 mg per kg of body weight, up to a maximum of 300 mg, per day divided doses. The dosage may be increased, if tolerated, after three days to 16 mg per kg of body weight, up to a maximum of 400 mg, per day. After three more days, if tolerated, the dosage may be increased to 20 mg per kg of body weight up to a maximum of 600mg, per day. One-half of the daily theophylline dose may be given at twelve-hour intervals. However, younger patients may require dosing at eight-hour intervals.

Duration

Variable, up to 24 hours
8. Summary of comparative effectiveness in a variety of clinical settings:

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Asthma: Overview

Asthma is a chronic inflammatory disease of the airways associated with airway hyperresponsiveness which induces airflow limitation. The airways are hyperresponsive to sorts of inhalational stimuli: cough, wheezing, and dyspnea develop paroxysmally. Airflow limitation ranges from mild to fatal, recovers spontaneously or by treatment and is, therefore, reversible. In the airways of patients who are affected with asthma for a long period of time, the airway walls thicken in the repeated processes of inflammation and its repair, resulting in decreased reversibility of airflow limitation and in increased airway hyperresponsiveness.

An international guideline for the treatment of asthma, the Global Initiative for Asthma (GINA), defines asthma as follows: “Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.”¹)

In patients who have died of asthma, the lung is overinflated, with both central and peripheral airways are full of mucous plugs which consist of mucus, serum protein, inflammatory cells, and tissue originating from necrocytosis. Usually, the airway lumen and airway walls are extensively infiltrated with eosinophils and lymphocytes. Mixtures of acute and chronic inflammation are inhomogeneously distributed throughout the airways.

Repeated airway inflammation in patients with asthma leads to progression in fibrosis, hypertrophies smooth muscle which contracts the bronchi, and increases the mucous plug, thus resulting in thickened and hardened bronchial walls; the inner diameter of the bronchi becomes narrow gradually. An increase in sputum production further limits airflow, provoking dyspnea. These inflammatory processes result in the release of physiologically active substances, e.g., a variety of cytokines and chemoreceptors, principally in the bronchial mucosa, and enhanced airway hyperresponsiveness is thus considered to develop. In the treatment of asthma, it is important to suppress this airway inflammation concurrently with the dilation of bronchi.

REFERENCE

1. Clinical pharmacology of theophylline

i) Bronchodilating activity of theophylline
Sustained-release theophylline is a potent bronchodilator and is widely used as a long-acting, reliable drug. As illustrated in the figure below, the administration of theophylline to patients with asthma is known to improve pulmonary function in a blood theophylline concentration-dependent manner.

In Appendix (1) are mentioned the papers which have examined the bronchodilating activity of theophylline. Its mechanism of action consists in an increase in bronchial smooth muscle cell c-AMP concentration due to phosphodiesterase (PDE)-inhibitory activity. Apart from this theory, sorts of theories including antagonistic activity on the adenosine receptor are available.

![Figure 3. Dose-Response Relation for Changes in Forced Expiratory Volume in the First Second (ΔFEV₁) against the Plasma Theophylline Concentration Plotted Semi-logarithmically. Plots for each subject are presented individually (-----0-----), as well as the unweighted least squares regression line for the whole group (-----). For each subject the ΔFEV₁ is normalized by division of the mean difference from the placebo value at each drug concentration plateau by the predicted value minus the placebo value.](image)

ii) Anti-inflammatory activity
In parallel with emphasis given to airway inflammation as the fundamental pathology of asthma, reports describing that theophylline also has anti-inflammatory activity similarly to steroids have been accumulated. Preclinical studies have reported inhibition of prolonged eosinophil survival at the time of stimulation with IL-5, inhibition of adhesion molecules on eosinophil, and others. In the clinical settings, theophylline is known to have inflammatory cell-inhibitory effects, e.g., a decrease in eosinophil count in the airways. Clinical reports are summarized in Appendix (2). It is noteworthy that many reports have described this effect at blood theophylline concentrations of 5 to 10 µg/mL after administration at relatively low doses (up to 400 mg/day). In recent years, theophylline has
been indicated to possibly enhance its anti-inflammatory activity in an additive fashion\(^9\). Theophylline is thus a potent bronchodilator and is concurrently a unique drug which has dual (bronchodilating and anti-inflammatory) activity.

### iii) Comparison between theophylline and steroids

#### (1) Efficacy equivalent to that of low-dose inhaled steroids

Inhaled steroids constitute the core in the current treatment of asthma. Therefore, we searched for reports which compared theophylline with inhaled steroids with respect to their clinical efficacy. Consequently, there were 3 reports which described the superiority of inhaled steroids to theophylline\(^{9,10,11}\) and 3 reports which found no large difference between inhaled steroids and theophylline\(^{12,13,14}\). Furthermore, there was a report which described the superiority of inhaled steroids to theophylline, although there was no large difference in efficacy\(^{15}\). None of the reports found serious adverse events in sustained-release theophylline. In Appendix (3) are mentioned the papers which compared theophylline with low-dose inhaled corticosteroids and which indicated that there was no large difference in efficacy. Thus, theophylline may be considered to be a drug which can be used as an alternative to low-dose inhaled corticosteroids. GINA shows that theophylline is an optional alternative to inhaled corticosteroids in mild persistent-type asthma at Step 2\(^1\).

#### (2) Combination of theophylline and steroids

##### (a) More potent efficacy than double doses of low- to middle-dose inhaled steroids

In the treatment of moderate or severer asthma, it is considered desirable in the aspects of efficacy and safety, as shown in GINA, to add other classes of antiasthmatic drugs rather than increasing the dose of an inhaled steroid alone. Among the other classes of antiasthmatic drugs about which such effect has been shown (theophylline, long-acting \(\beta_2\) stimulants, and leukotriene receptor antagonists), theophylline is the only drug which is currently included in essential drugs of the WHO. In Appendix (4) are summarized the studies which compared the combination of theophylline and low-dose inhaled steroids with dose increases in inhaled steroids. Theophylline is considered an essential drug also from this viewpoint.

##### (b) Add-on effect of theophylline on middle- to high-dose inhaled steroids

The additional use of theophylline is known to be effective also for severe asthma, and theophylline is a drug which could be added to a high-dose inhaled steroid. In Appendix (5) are shown reports which have described the combination of high-dose inhaled steroids and theophylline.
Furthermore, the efficacy of theophylline addition in severe asthma patients who are using oral steroids is also known\textsuperscript{16,17}. There is a report which has described that the additional administration of theophylline or placebo to steroid-dependent asthmatic children increased the number of days free of symptoms in the theophylline group compared to the placebo group and provoked a two-fold increase in the frequency of per-request use of inhaled $\beta_2$ stimulants and a three-fold increase in the additional need for steroids in the placebo group\textsuperscript{18}.

Currently, theophylline is the only oral drug with anti-inflammatory activity among essential drugs. Therefore, theophylline becomes important in patients who have poor compliance with inhaled steroids. There is a report which has described that compliance is superior with oral theophylline to with inhaled steroids or DSCG\textsuperscript{19}. Furthermore, there are many children and others who cannot inhale the drug capably. Inhaled drugs are adversely affected by technical issues, i.e., skilled or unskilled inhalation, and, therefore, possibly fail to exert their actions in patients with unskilled inhalation.

Importantly, inhaled drugs which require administration via airways are considered:
1) to have weak effects on muscle layers, although theoretically they reach airway mucosa; and
2) to present a low small airway reach rate.
Oral drugs are free of this problem because they are delivered to the whole body. Oral drugs have a major role also based on this difference. Theophylline is the only oral drug among essential drugs in the category of antiasthmatic drugs. Therefore, it would be reasonable to preserve theophylline.

**REFERENCE**


19) Kelloway JS et al.: Comparison of patients' compliance with prescribed oral and inhaled asthma medications. Arch Intern Med. 154(12):1349-52. 1994
2. Clinical effects of theophylline

We searched for papers on the clinical effects of theophylline in PubMed, with keywords of “theophylline” and “asthma” and with search restriction to “clinical trials”. We summarize below the results of the search by item.

i) Improvement of asthmatic symptoms and respiratory function (particularly, nocturnal symptoms)

The efficacy of treatment with theophylline has been examined from old times. Especially, there are many clinical reports which have described nocturnal asthma for which sustained-release preparations were used; the reports have shown inhibited variations of PEF, a decrease in the number of per-request uses of inhaled $\beta_2$ stimulants, and others$^{20,21,22,23,24,25,26,27}$. An 8-week, placebo-controlled, double-blind study in 73 patients with asthma has indicated an improvement in cough, wheezing, nocturnal sleep disorder, and PEFR and has stated that the overall impression of patients and physicians toward theophylline was favorable$^{24}$.

ii) Inhibitory effect on late asthmatic response

Many of patients with asthma are affected with atopic asthma, and patients with atopic asthma show a biphasic decrease in pulmonary function due to the inhalation of antigens. This biphasic response is called immediate asthmatic response and late asthmatic response (LAR). LAR is considered to be associated with the exacerbation of persisting symptoms. The administration of theophylline has been reported to inhibit LAR$^{28,29,30,31,32,33}$.

Pauwels et al. have examined the LAR-inhibitory effect of theophylline in 9 patients. Theophylline was administered intravenously since 1 hour prior to challenge with the antigen, and a 6-hour continuous intravenous infusion was conducted after loading dose for 60 minutes. Consequently, theophylline significantly inhibited LAR$^{31}$. A similar review has been made also for sustained-release theophylline. Sullivan et al. have reported that the 6-week administration of sustained-release theophylline 400 mg/day inhibited LAR and simultaneously suppressed airway infiltration by eosinophils$^{32}$.

iii) Inhibition of exercise-induced asthma

We searched for studies on exercise-induced asthma. Consequently, 6 reports have shown the inhibitory effect of theophylline on pulmonary function decrease after exercise stress$^{33,34,35,36,37,38}$. In a study which was conducted in patients with airway hyperresponsiveness to methacholine or with exercise-induced airway obstruction, a
significant increase in methacholine PC20 and significant inhibition of the FEV\textsubscript{1} maximum decrease rate after exercise stress were observed in the theophylline plain tablet single administration group or the 1-week sustained-release theophylline administration group compared to the placebo group\textsuperscript{37}. This inhibitory effect is considered to be concentration-dependent. The reducing effect of the single intravenous administration of both theophylline 200 mg (mean blood concentration: 6.7 µg/mL) and 351 mg (mean blood concentration: 10.1 µg/mL) on exercise stress-induced airway obstruction was significant. However, higher efficacy was observed with theophylline 351 mg\textsuperscript{38}.

Among the studies which reported the EIA-inhibitory effect of β\textsubscript{2} stimulants and theophylline, we discovered 4 reports which found no difference in efficacy between them\textsuperscript{39,40,41,41}. Among the studies which examined the EIA-inhibitory effect of DSCG and theophylline, there was 1 report which found no difference\textsuperscript{42}. Among the studies which used nonsustained-release theophylline, we discovered 1 report which found slight advantage in favor of DSCG\textsuperscript{40}.

Theophylline has been thus demonstrated to be an important drug also from the viewpoint of EIA-inhibitory effect.

iv) Inhibition of asthma effects on school, job, and others, as well as improvement of QOL

Impairment of going to school or job by asthmatic symptoms constitutes a great problem for patients with asthma. In a study which compared the 1-year efficacy of theophylline (adjusted to 8 to 15 µg/mL in blood concentration) and beclomethasone (336 µg/day), the percentages of patients who failed to attend job or school by 1 or more days were 23% and 24%, respectively; no difference was reported\textsuperscript{15}. In a similar study in children, there was no significant difference between theophylline and beclomethasone with respect to the percentages of patients who failed to attend school by 1 or more days\textsuperscript{14}. These results lead us to consider that theophylline is comparable to beclomethasone with respect to inhibition of asthma effects on school, job, and others.

A study in Japan which used an originally prepared questionnaire for caregivers of children with asthma has reported the QOL-improving effect of theophylline\textsuperscript{44}. Furthermore, there is a study which compared a long-acting β\textsubscript{2} stimulant salmeterol with theophylline to evaluate QOL by the Living with Asthma questionnaire, indicated an improvement by the administration of each drug and found no significant difference between the drugs in terms of their efficacy\textsuperscript{45}. In a study which compared zyleuton (5-lipoxygenase inhibitor) and theophylline, both drugs improved QOL equally\textsuperscript{46}. These results indicated that theophylline is a drug which contributes to an improvement in QOL.

v) Theophylline as a bronchodilator (comparison with β\textsubscript{2} stimulants)
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We searched for papers which compared theophylline with β2 stimulants, e.g., terbutaline and metaproterenol, apart from salbutamol—considered to be an essential drug. We excluded long-acting β2-stimulants, salmeterol and formoterol, because they largely differ from salbutamol in duration of action. Furthermore, we also excluded papers whose abstract had no definite results of comparison between both drugs. We excluded the comparison in exercise-induced asthma because we had examined it in another clause.

Consequently, 12 of 13 reports obtained described that theophylline is nearly comparable or superior to β2 stimulants. The remaining 1 report stated that 11 of 15 patients preferred salbutamol but found no difference in pulmonary function. Furthermore, a study which compared sustained-release theophylline with inhaled salbutamol reported that the inhibitory effect on histamine-induced airway constriction was more potent with salbutamol than with sustained-release theophylline but its effect disappeared in 4 hours and that the inhibitory effect of theophylline was maintained also at that time, on the other hand. There is no report which has described that theophylline is obviously inferior to salbutamol.

In addition, there are many reports which have described that the combination of theophylline with β2 stimulants is effective. There are also reports which have described that theophylline, when combined at half the dose, shows equivalent or greater efficacy compared to theophylline alone or β2 stimulant alone.

REFERENCE
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1998

49) Schuller DE et al.: A comparison of metaproterenol and theophylline for control of


3. Positioning in guidelines

i) Positioning in Expert Panel Report 2
Expert Panel Report 2[^69], a US guideline for asthma, has mentioned theophylline as one of options for mild, persistent asthma (Step 2), and its combination with an inhaled steroid for moderate to severe asthma (Step 3-4) in adults. In children it mentions the combination of theophylline with an inhaled steroid as an option in moderate asthma (Step 3).

ii) Global Initiative for Asthma (GINA 2003)[^70]
GINA, an international guideline, defines that sustained-release theophylline is a drug which can be used as a controller for both adults and children. Step 2 Mild Persistent mentions theophylline as one of therapeutic options which surrogate a low-dose inhaled steroid. Step 3 Moderate Persistent and Step 4 Severe Persistent mentions that theophylline is a drug which is to be combined with a low-dose inhaled steroid.

iii) Japanese guideline for asthma (JGL 1998)[^70]
Japanese guideline for asthma positions that sustained-release theophylline is a drug which can be administered alone for adult patients with mild persisting asthma (Step 2) and is a long-term control drug which is to be combined with an inhaled steroid for patients with moderate to severe asthma (step 3-4). This guideline has indicated that the administration of theophylline may be considered also for mild intermittent asthma, depending on patients. The guideline defines that theophylline (xanthine agent) is a drug which can be used for patients with mild persistent or severer asthma.

As described above, all the guidelines include the use of sustained-release theophylline. Thus, the use of theophylline in the treatment of asthma is accepted in countries.

REFERENCE
Application for the Inclusion of Theophylline in the WHO Model List of Essential Medicines

i) Expert Panel Report 2

**Figure 3.4b: Stepwise Approach for Managing Asthma in Adults and Children Older Than 5 Years of Age: Treatment (Continued)**

<table>
<thead>
<tr>
<th>Long-Term Control</th>
<th>Quick Relief</th>
<th>Education</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STEP 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild Persistent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>one daily medication:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>anti-inflammatory:</td>
<td>either inhaled corticosteroid (low dose) or cromolyn or nedocromil (children usually begin with a trial of cromolyn or nedocromil)</td>
<td></td>
</tr>
<tr>
<td>Sustained-release theophylline to serum concentration of 5-15 mcg/mL is a hallmark, but not preferred therapy.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attributable or severe may also be considered for patients &gt;12 years of age, although their position in therapy is not fully established</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>STEP 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild Intermittent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No daily medication needed.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting bronchodilator inhaled beta-agonists as needed for symptoms.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensity of treatment will depend on severity of exacerbation; see component 3 Managing Exacerbations.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of short-acting inhaled beta-agonists more than 2 times a week may indicate the need for asthma long-term control therapy.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teach basic facts about asthma</td>
<td>Teach inhaler/spacer holding chamber technique</td>
<td></td>
</tr>
<tr>
<td>Teach inhaler/spacer holding chamber technique</td>
<td>Discuss roles of medications</td>
<td></td>
</tr>
<tr>
<td>Develop self-management plan</td>
<td>Develop action plan for when and how to take rescue actions, especially for patients with a history of severe exacerbations</td>
<td></td>
</tr>
<tr>
<td>Discuss appropriate environmental control measures to avoid exposure to known allergens and irritants (see component 4).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Step down**
Review treatment every 1 to 6 months, a gradual response in treatment may be possible.

**Step up**
If control is not maintained, consider step up. First, review patient medication technique, adherence, and environmental control. Avoidance of allergens or other factors that contribute to asthma severity.

**NOTE:**
- The stepwise approach provides general guidelines to assist clinical decision-making and is not intended to be a specific prescription. Asthma is highly variable, clinicians should tailor specific medication plans to the needs and circumstances of individual patients.
- Care control as quickly as possible, then decrease treatment to the least medication necessary to maintain control. Gaining control may be accomplished by either starting treatment at the step most appropriate to the initial severity of the condition or starting at a higher level of therapy (e.g., a course of systemic corticosteroids).
- A course of systemic corticosteroids may need to be prolonged in some cases.
- Some patients with intermittent asthma experience severe and life-threatening exacerbations separated by long periods of normal lung function and no symptoms. This may happen especially with exacerbations provoked by respiratory infections. A short course of systemic corticosteroids is recommended.
- As such, patients should control their environment to avoid or control factors that make their asthma worse (e.g., allergens, irritants); this requires specific diligence and education.
- Referral to an asthma specialist for consultation or management is recommended if there are difficulties achieving or maintaining control of asthma or if the patient requires step 4 care. Referral may be considered if the patient requires step 3 care (see component 1 Initial Assessment and Diagnosis).
Application for the Inclusion of Theophylline in the WHO Model List of Essential Medicines

i) Expert Panel Report 2

<table>
<thead>
<tr>
<th>Step 4</th>
<th>Long-Term Control</th>
<th>Quick Relief</th>
<th>Education</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Persistent</td>
<td>Daily medications:</td>
<td>Short-acting bronchodilator; inhaled beta-agonists as needed for symptoms.</td>
<td>Steps 2 and 3 actions plus: Refer to individual education/counseling</td>
</tr>
<tr>
<td></td>
<td>Anti-inflammatory: inhaled corticosteroid (high dose) AND</td>
<td>Intensity of treatment will depend on severity of exacerbation; see component 3 Managing Exacerbations.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Long-acting bronchodilator; either long-acting inhaled beta-agonist, sustained-release theophylline, or long-acting beta-agonist tablets AND</td>
<td>Use of short-acting inhaled beta-agonists on a daily basis, or increasing use, indicates the need for additional long-term-control therapy.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Corticosteroid tablets or syrup long term (make repeat attempts to reduce systemic steroids and maintain control with high dose inhaled steroids)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 3</th>
<th>Long-Term Control</th>
<th>Quick Relief</th>
<th>Education</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate Persistent</td>
<td>Daily medication:</td>
<td>Short-acting bronchodilator; inhaled beta-agonists as needed for symptoms.</td>
<td>Step 1 actions plus:</td>
</tr>
<tr>
<td></td>
<td>Either:</td>
<td>Intensity of treatment will depend on severity of exacerbation; see component 3 Managing Exacerbations.</td>
<td>Teach self-monitoring</td>
</tr>
<tr>
<td></td>
<td>Anti-inflammatory: inhaled corticosteroid (medium dose) OR</td>
<td>Use of short-acting inhaled beta-agonists on a daily basis, or increasing use, indicates the need for additional long-term-control therapy.</td>
<td>Refer to group education if available</td>
</tr>
<tr>
<td></td>
<td>Inhaled corticosteroid (low-medium dose) and add a long-acting bronchodilator, especially for nighttime symptoms; either long-acting inhaled beta-agonists, sustained-release theophylline, or long-acting beta-agonist tablets.</td>
<td></td>
<td>Review and update self-management plan</td>
</tr>
<tr>
<td></td>
<td>If needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anti-inflammatory: inhaled corticosteroids (medium-high dose) AND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Long-acting bronchodilator, especially for nighttime symptoms; either long-acting inhaled beta-agonists, sustained-release theophylline, or long-acting beta-agonist tablets.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Application for the Inclusion of Theophylline in the WHO Model List of Essential Medicines

i) Expert Panel Report 2
### Recommended Medications by Level of Severity:
#### Adults and Children Older Than 5 Years of Age (GINA Updated 2003)

All Levels: In addition to regular daily controller therapy, rapid-acting inhaled β2-agonist* should be taken as needed to relieve symptoms, but should not be taken more than 3 to 4 times a day. Patient education is essential at every level.

<table>
<thead>
<tr>
<th>Level of Severity</th>
<th>Daily Controller Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1:</strong> Intermittent Asthma***</td>
<td>· None necessary</td>
</tr>
<tr>
<td><strong>Step 2:</strong> Mild Persistent</td>
<td>· Low-dose inhaled glucocorticosteroid</td>
</tr>
<tr>
<td><strong>Step 3:</strong> Moderate Persistent</td>
<td>· Low-to-medium inhaled glucocorticosteroid plus long-acting inhaled β2-agonist</td>
</tr>
</tbody>
</table>
| **Step 4:** Severe Persistent | · High-dose inhaled glucocorticosteroid plus long-acting inhaled β2-agonist plus one or more of the following, if needed:
  · Sustained-release theophylline
  · Leukotriene modifier
  · Long-acting inhaled β2-agonist
  · Oral glucocorticosteroid |

**Other Treatment Options**
- Sustained-release theophylline, or
- Cromone, or
- Leukotriene modifier

All Levels: Once control of asthma is achieved and maintained for at least 3 months, gradual reduction of maintenance therapy should be tried in order to identify the minimum therapy required to maintain control.

* Other options for reliever medication are (in increasing order of cost) inhaled anticholinergic, short-acting oral β2 agonist, and short-acting theophylline.

** Other treatment options listed in order of increasing cost. Relative medication costs may vary from country to country.

*** Patients with intermittent asthma but severe exacerbations should be treated as having moderate persistent asthma (Evidence D)
### Recommended Medications by Level of Severity: Children Younger Than 5 Years of Age (GINA Updated 2003)

All Levels: In addition to regular daily controller therapy, rapid-acting inhaled β₂-agonist* should be taken as needed to relieve symptoms, but should not be taken more than 3 to 4 times a day. Patient education is essential at every level.

<table>
<thead>
<tr>
<th>Level of Severity</th>
<th>Daily Controller Medications</th>
<th>Other Treatment Options**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1: Intermittent Asthma***</td>
<td>None necessary</td>
<td></td>
</tr>
<tr>
<td>Step 2: Mild Persistent</td>
<td>Low-dose inhaled glucocorticosteroid</td>
<td>Sustained-release theophylline, or Cromone, or Leukotriene modifier</td>
</tr>
<tr>
<td>Step 3: Moderate persistent</td>
<td>Medium-dose inhaled glucocorticosteroid</td>
<td>Medium-dose inhaled glucocorticosteroid plus sustained-release theophylline, or Medium-dose inhaled glucocorticosteroid plus long-acting oral β₂-agonist, or High-dose inhaled glucocorticosteroid, or Medium-dose inhaled glucocorticosteroid plus leukotriene modifier</td>
</tr>
<tr>
<td>Step 4: Severe persistent</td>
<td>High-dose inhaled glucocorticosteroid plus long-acting inhaled β₂-agonist plus one or more of the following, if needed: Sustained-release theophylline Leukotriene modifier Long-acting inhaled β₂-agonist Oral glucocorticosteroid</td>
<td></td>
</tr>
</tbody>
</table>

All Levels: Once control of asthma is achieved and maintained for at least 3 months, gradual reduction of maintenance therapy should be tried on order to identify the minimum therapy required to maintain control.

* Other options for reliever medication are (in increasing order of cost) inhaled anticholinergic, short-acting oral β₂ agonist, and short-acting theophylline.

** Other treatment options listed in order of increasing cost. Relative medication costs may vary from country to country.

*** Patients with intermittent asthma but severe exacerbations should be treated as having moderate persistent asthma (Evidence D)
iii) Japanese guideline for asthma (JGL 1998)

<table>
<thead>
<tr>
<th>Disease severity</th>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild intermittent asthma</td>
<td>Mild persistent asthma</td>
<td>Moderate persistent asthma</td>
<td>Severe persistent asthma</td>
</tr>
<tr>
<td>Clinical features</td>
<td>wheezing, cough, and dyspnea for more than 3 days per week</td>
<td>Asthma attacks at least 3 times per week</td>
<td>Chronic asthma symptoms</td>
<td>Frequent asthma exacerbations</td>
</tr>
<tr>
<td></td>
<td>Symptomatic bronchial obstruction</td>
<td>Occasional difficulty sleeping and limitation of daily activities at least 2 times per month</td>
<td>Inhaled β₂ agonist required almost daily</td>
<td>Persistent symptoms</td>
</tr>
<tr>
<td></td>
<td>Nocturnal symptoms 3 or more than 1 or 2 time per month</td>
<td>Nocturnal symptoms 3 or more than 1 or 2 times per month</td>
<td>Symptom limitation of daily activities at least once a week</td>
<td>Limitation of daily activities</td>
</tr>
<tr>
<td></td>
<td>PEF, FEV₁</td>
<td>70% or higher of personal best or predicted value</td>
<td>60% or lower of personal best or predicted value</td>
<td>&lt;60% of personal best or predicted value</td>
</tr>
<tr>
<td></td>
<td>Variation of &lt;20%</td>
<td>Variation of &lt;10%</td>
<td>Variation of &gt;30%</td>
<td>Variation of &gt;30%</td>
</tr>
<tr>
<td>Treatment</td>
<td>Inhaled or oral β₂ agonist or theophylline as needed</td>
<td>Daily use of an inhaled corticosteroid (low dose)</td>
<td>Daily use of an inhaled corticosteroid (high dose)</td>
<td>Daily use of an inhaled corticosteroid (high dose)</td>
</tr>
<tr>
<td></td>
<td>Inhaled β₂ agonist or ipratropium before exercise or exposure to allergens</td>
<td>Daily use of an inhaled corticosteroid (low dose)</td>
<td>Daily use of an inhaled corticosteroid (high dose)</td>
<td>Daily use of an inhaled corticosteroid (high dose)</td>
</tr>
<tr>
<td></td>
<td>Oral theophylline or montelukast</td>
<td>Daily use of an inhaled corticosteroid (low dose)</td>
<td>Daily use of an inhaled corticosteroid (high dose)</td>
<td>Daily use of an inhaled corticosteroid (high dose)</td>
</tr>
<tr>
<td></td>
<td>Daily administration of sustained-release theophylline</td>
<td>Daily administration of azaclamide, oral or inhaled β₂ agonist</td>
<td>Daily administration of azaclamide, oral or inhaled β₂ agonist</td>
<td>Daily administration of azaclamide, oral or inhaled β₂ agonist</td>
</tr>
<tr>
<td></td>
<td>Daily administration of azaclamide, oral or inhaled β₂ agonist</td>
<td>Daily administration of azaclamide, oral or inhaled β₂ agonist</td>
<td>Daily administration of azaclamide, oral or inhaled β₂ agonist</td>
<td>Daily administration of azaclamide, oral or inhaled β₂ agonist</td>
</tr>
</tbody>
</table>

| Additional use of an inhaled β₂ agonist as needed (maxim. of 3 to 4 times per day) | Additional use of an inhaled β₂ agonist as needed (maxim. of 3 to 4 times per day) | Additional use of an inhaled β₂ agonist as needed (maxim. of 3 to 4 times per day) | Additional use of an inhaled β₂ agonist as needed (maxim. of 3 to 4 times per day) |

Any one of the findings marked with a solid square (□) rates the patient at that step. Overlapping findings (also marked with a solid square) rate the patient at the more severe step. These symptoms and pulmonary function test findings are used to rate the approximate step of asthma severity. These symptoms and findings may change and there may be an overlap between steps.

- Patients with wheezing or coughing only may have been daily or weekly, as indicated in the dosing instructions below.
- The patient should use a spacer device for administration of inhaled corticosteroids.
- The patient should be monitored for adverse effects.

Step-Up: Treatment should be stepped up if symptoms are not controlled with current treatment. (For patients with a PEF of <60%, treatment should be stepped up after administration of a short course of prednisone to high dose corticosteroids.)

Step-Down: Treatment may be stepped down if adverse effects or respiratory symptoms are controlled. Clenbuterol or beclomethasone may be used for maintenance therapy with a gradual decrease in dosage over a period of weeks.

Step-Off: Treatment is continued for at least 3 months. Treatment required to maintain control of symptoms should be continued.
iii) Japanese guideline for asthma (Japanese guideline for pediatric asthma 2004)

### Long-term management of childhood asthma (6-15 years)

<table>
<thead>
<tr>
<th>Classification</th>
<th>First treatment choice</th>
<th>Other treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1: Intermittent</td>
<td>No ICS necessary</td>
<td>anti-allergic drug (considered)</td>
</tr>
<tr>
<td>Step 2: Mild Persistent</td>
<td>ICS ≤ 200 µg</td>
<td>DSCG and/or SRT and/or LABA plus (considered)</td>
</tr>
<tr>
<td>Step 3: Moderate Persistent</td>
<td>ICS ≤ 400 µg</td>
<td>DSCG and/or SRT and/or LABA</td>
</tr>
<tr>
<td>Step 4: Severe Persistent</td>
<td>ICS ≤ 800 µg</td>
<td>DSCG and/or SRT and/or LABA and/or LTRA</td>
</tr>
</tbody>
</table>

ICS, inhaled corticosteroid (dose of ICS is BDP [CFC-pMDI] or equivalent); LTRA, leukotriene receptor antagonists; DSCG, disodium cromoglycate; SRT, sustained-release theophylline; LABA, long acting β₂ agonist.

### Long-term management of childhood asthma (2-5 years)

<table>
<thead>
<tr>
<th>Classification</th>
<th>First treatment choice</th>
<th>Other treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1: Intermittent</td>
<td>None</td>
<td>anti-allergic drug (considered)</td>
</tr>
<tr>
<td>Step 2: Mild Persistent</td>
<td>DSCG+β₂-agonist and/or anti-allergic drug</td>
<td>SRT ICS ≤ 200 µg considered</td>
</tr>
<tr>
<td>Step 3: Moderate Persistent</td>
<td>ICS ≤ 300 µg</td>
<td>plus (considered) DSCG+β₂-agonist and/or SRT and/or LABA</td>
</tr>
<tr>
<td>Step 4: Severe Persistent</td>
<td>ICS ≤ 600 µg</td>
<td>plus SRT and/or LTRA and/or DSCG +β₂-agonist and/or LABA</td>
</tr>
</tbody>
</table>

ICS, inhaled corticosteroid (dose of ICS is BDP [CFC-pMDI] or equivalent); LTRA, leukotriene receptor antagonists; DSCG, disodium cromoglycate; SRT, sustained-release theophylline; LABA, long acting β₂ agonist.

### Long-term management of childhood asthma (<2 years)

<table>
<thead>
<tr>
<th>Classification</th>
<th>First treatment choice</th>
<th>Other treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1: Intermittent</td>
<td>None</td>
<td>anti-allergic drug (considered)</td>
</tr>
<tr>
<td>Step 2: Mild Persistent</td>
<td>anti-allergic drug</td>
<td>DSCG+β₂-agonist and/or SRT ICS ≤ 100 µg considered</td>
</tr>
<tr>
<td>Step 3: Moderate Persistent</td>
<td>ICS ≤ 200 µg</td>
<td>plus (considered) DSCG+β₂-agonist and/or SRT and/or LABA</td>
</tr>
<tr>
<td>Step 4: Severe Persistent</td>
<td>ICS ≤ 400 µg</td>
<td>plus SRT and LTRA and/or DSCG+β₂-agonist and/or LABA</td>
</tr>
</tbody>
</table>

ICS, inhaled corticosteroid (dose of ICS is BDP [CFC-pMDI] or equivalent); LTRA, leukotriene receptor antagonists; DSCG, disodium cromoglycate; SRT, sustained-release theophylline; LABA, long acting β₂ agonist.
4. Positioning in chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a disorder which is characterized by not completely reversible airflow limitation. Airflow limitation is usually progressive and associated with abnormal inflammatory responses of lungs to hazardous substances and gas. Bronchodilators constitute the core of the treatment of COPD symptoms and are administered as needed or as consecutive treatment to alleviate and prevent symptoms. Fundamentally, bronchodilators include $\beta_2$ stimulants, anticholinergic drugs, theophylline, and the combination thereof.

Global Initiative for Obstructive Lung Disease (GOLD) describes that the selection of $\beta_2$ stimulants, anticholinergic drugs, sustained-release theophylline, or combined treatment depends on availability and individual response in terms of symptom relief and side effects\(^{71}\). The guideline defines that these long-acting bronchodilators are used in Step 2 Moderate or in severer disease.

The Japanese Respiratory Society guideline\(^{72}\) defines, similarly to GOLD, that sustained-release theophylline is to be a long-acting bronchodilator which is used from Step 2 Moderate like as $\beta_2$ stimulants and anticholinergic drugs. The European Respiratory Society guideline\(^{73}\) and the American Thoracic Society guideline\(^{74}\) describe theophylline as a drug which is to be followed anticholinergic drugs and $\beta_2$ stimulants. The use of theophylline for COPD is thus recognized in guidelines of countries.

In Appendix (6) are mentioned the reports on the clinical pharmacology and clinical efficacy.
of theophylline in COPD. Theophylline, apart from being effective when used alone, has shown combination effects with anticholinergic drugs or β2 stimulants in COPD in which there are many opportunities for multiple drug combination in patients with severe disease. Furthermore, theophylline has been suggested to be effective also for airway inflammation in COPD. As described previously, furthermore, compliance is better with oral drugs. Theophylline is the only oral agent among essential drugs also in COPD.

REFERENCE
Conclusion

In conclusion, theophylline is an effective drug with bronchodilating and anti-inflammatory effects and can be used alone or in combination in asthma and COPD. Its safety has been verified. Theophylline is the only oral agent among the essential drugs in asthma and COPD. Current international and national guidelines for asthma and COPD have recommended sustained release theophylline for long-term control of these diseases. Therefore, it is concluded that theophylline should be retained as essential drug in the WHO Model List.
**Theophylline as a bronchodilator**

**Rational Intravenous Doses of Theophylline.**


Summary:
Physiologic responses to intravenously administered theophylline were determined in nine hospitalized asthmatic subjects. Continuous improvement in vital capacity and first-second forced expiratory volume was observed over the plasma range of theophylline concentration of 5 to 20 mg per liter. The improvement varied directly with the logarithm of the plasma concentration.

**Evaluation of oral bronchodilator therapy in asthmatic children. Bronchodilators in asthmatic children.**


Summary:
The bronchodilator efficacy of oral ephedrine and theophylline (as aminophylline) was examined in a randomized double-blind study. Week-long trials of five drug regimens were administered every 6 hours to 12 asthmatic children. These regimens included conventional and “high” (approximately twice conventional) doses of the two-drug combination and “high” doses of the individual drugs. Aminophylline in “High” doses (serum theophylline concentration 13 μg/mL) was highly effective in relieving signs and symptoms of asthma.

**Analysis of pulmonary function testing**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ephedrine and aminophylline (low dose)</th>
<th>Ephedrine (high dose)</th>
<th>Aminophylline (high dose)</th>
<th>Ephedrine and aminophylline (high dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF</td>
<td>Mean</td>
<td>1.61</td>
<td>1.85</td>
<td>1.98</td>
<td>2.20</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td></td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MFR</td>
<td>Mean</td>
<td>3.31</td>
<td>3.65</td>
<td>3.98</td>
<td>4.34</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td></td>
<td>&gt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FEV1</td>
<td>Mean</td>
<td>1.11</td>
<td>1.27</td>
<td>1.29</td>
<td>1.46</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td></td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FVC</td>
<td>Mean</td>
<td>1.57</td>
<td>1.69</td>
<td>1.79</td>
<td>1.93</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td></td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

The P value express the probability of each regimen mean differing from the placebo.

Apart from these papers, there many studies comparing theophylline with bronchodilators β₂ stimulants in terms of their clinical efficacy which indicated that theophylline has efficacy which is equivalent to that of β₂ stimulants in improving pulmonary function (Table 2-V) (see Theophylline as a bronchodilator (comparison with β₂ stimulants)).
**Effect of theophylline on airway inflammation**

**Effect of Slow-Release Theophylline on Airway Inflammation in Bronchial Asthma**
Adachi M et al.: Allergy 47,8: 734-743, 1998

Summary:
Asthma symptom score was significantly improved after theophylline treatment. Significant decreases in the percentages of total and EG2+ eosinophils in induced sputum demonstrated that slow-release theophylline has anti-inflammatory effect in patients with asthma.

**Effect of Theophylline Withdrawal on Airway Inflammation in Asthma**

Summary:
Patients by treatment with both a moderate dose of inhaled corticosteroids (BDP) 400 µg/day) and low dose theophylline were investigated. In the theophylline withdrawal group, there were small but significant falls in PEF in the morning, FEV\(_1\) and \(V_{50}\) at the end of the study period. Analysis of induced sputum showed that there was also a significant increase in the percentage of total and activated (EG2+) eosinophils only in those patients who withdrew from theophylline.

**Anti-inflammatory effects of low-dose oral theophylline in atopic asthma.**

Summary:
A study of the effect of oral theophylline on the inflammatory response of the bronchial mucosa to inhalation of allergen showed significant reduction in number of EG2+ eosinophils and total eosinophils after treatment with theophylline 400 mg/day. The mean serum concentration was 6.7 mcg/mL.
Theophylline Has a Dose-related Effect on the Airway Response to inhaled Histamine and Methacholine in Asthmatics.


Summary:
Inhalation challenges with histamine and methacholine was performed after placebo and after intravenous theophylline ethylenediamine given. At a mean serum concentration of 6.14 mcg/ml, theophylline increased geometric mean PD$_{100}$ Sraw for histamine from 2.76 to 6.07 units and for methacholine from 1.52 to 2.60 units. At a mean serum concentration of 12.9 mcg/ml, theophylline increased geometric mean PD$_{100}$ Sraw for histamine from 2.70 to 17.1 units and for methacholine from 1.28 to 4.98 units. There was a protective effect of theophylline on histamine and methacholine responsiveness in asthma patients.

Effect of chronic theophylline treatment on the methacholine dose-response curve in allergic asthmatic subjects.


Summary:
Thirty-six mild asthmatics were divided into two groups, one receiving theophylline and the other placebo to investigate the effect of theophylline on airway responsiveness. After 2 months of treatment with theophylline, there was a significant lowering of airway reactivity (slope) to methacholine and improvements in methacholine sensitivity (PC$_{20}$).

Theophylline: Potential antiinflammatory effects in nocturnal asthma.


Summary:
An anti-inflammatory effect of 2-week treatment of theophylline was evaluated in 8 patients with nocturnal asthma. Theophylline significantly improved the overnight decrement in lung function than placebo and also significantly decreased the percentage of neutrophils in the 4:00 AM BAL and stimulated leukotriene B4 levels from macrophages obtained at 4:00 AM.

Low-dose theophylline does not exert its anti-inflammatory effects in mild asthma through upregulation of interleukin-10 in alveolar macrophages.
Oliver B et al.: Allergy. 56(11): 1087-90, 2001

Summary:
In a study involving 15 steroid-free patients with mild asthma, there was a significant reduction in BAL eosinophil number after theophylline treatment compared with placebo. This effect is not mediated via the production of IL-10 or the attenuation of GM-CSF or TNF-alpha.

Controlled-release theophylline inhibits early morning airway obstruction and hyperresponsiveness in asthmatic subjects.

Summary:
Theophylline inhibits the development of airway obstruction and airway hyperresponsiveness early in the morning in 18 nocturnal asthma subjects. At 6 AM, both FEV₁ and PC₂₀FEV₁ were significantly higher on theophylline than on placebo. At 2 PM and 10 PM FEV₁, but not PC₂₀FEV₁, was higher on theophylline than on placebo.
Comparison of Theophylline with Low-dose Inhaled Corticosteroid

Theophylline vs. Budesonide in the Treatment of Mild to Moderate Bronchial Asthma

Summary:
Theophylline (mean plasma concentration: 11.9 ± 4.6 mcg/mL) vs. budesonide (800 mcg/day) in the treatment of 8 asthma patients was almost equal. PEF differences between morning and evening during theophylline vs. budesonide were not significant. Nausea was reported in 2 patients during theophylline treatment. Side effect of budesonide was not shown.

Aerosol Beclomethasone Dipropionate Compared With Theophylline as Primary Treatment of Chronic, Mild to Moderately Severe Asthma in Children

Summary:
Aerosol BDP (84 × 4 µg/day) and sustained-release theophylline (serum concentration 8-15 mcg/mL) were effective primary treatments for mild to moderate chronic asthma in children. No spontaneous reports of seizures, coma, gastrointestinal bleeding or paroxysmal tachycardia. More patients taking theophylline experienced headache, CNS side effects other than headache, tremor, gastric irritation, nausea and vomiting. Growth velocity suppression was noted with BDP and was more pronounced in boys. Mean change of height measurement between baseline and 12 months was 4.4 cm/year for BDP group and 6.0 cm/year for theophylline group. Difference between observed and predicted rates of growth was also significantly different between BDP group and Theophylline group.
Aerosol beclomethasone dipropionate spray compared with theophylline as primary treatment for chronic mild-to-moderate asthma.


Summary:
In 647 asthma patients (6 to 65 years of age) both of BDP (84 × 4 µg/day) and sustained-release theophylline (serum concentration 8-15 mcg/mL) were effective to maintain nearly normal pulmonary function, reduce symptom, achieved low absenteeism from work or school. BDP was more effective in reducing symptoms, supplemental bronchodilator and systemic glucocorticoid doses, bronchial hyperresponsiveness and eosinophilia, however the magnitude of these differences was small.

There were no life-threatening adverse effects attributable to the study medications. More patients taking theophylline had headaches, insomnia, tremor, nervousness, dizziness presumably, gastric irritation, dyspepsia, nausea, and vomiting. More patients taking BDP had oropharyngeal candidiasis, voice disturbance, hoarseness, and acute pharyngitis. The means of the morning cortisol levels were similar in the two groups at the beginning of the study, but by 6 and 12 months, they were lower in BDP group.

Efficacy of inhaled budesonide and oral theophylline in asthmatic subjects.


Summary:
Thirty-eight Patients with mild to moderate asthma were received inhaled budesonide 800 mcg/day or theophylline (serum concentration 5-15 mcg/mL). Both treatments were associated with significant decrease of symptom scores and increase in PEF and FEV₁. Blood and nasal eosinophils and serum IL-5 were also decreased in both treatment groups. Both budesonide and theophylline treatments were well tolerated. Nausea occurred in 1 patient receiving theophylline.
Comparative efficacy of once-daily therapy with inhaled corticosteroid, leukotriene antagonist or sustained-release theophylline in patients with mild persistent asthma.


Summary:
To compare the efficacy and safety of the inhaled budesonide, sustained-release theophylline and montelukast, a leukotriene receptor antagonist, 74 patients with mild persistent asthma were treated with either inhaled budesonide 400 µg once daily, oral montelukast 10 mg once daily, or sustained-release theophylline 400 mg once daily for 3 months. In all three treatment groups, improvements were attained in overall asthma control. Asthma symptom scores and supplemental beta-agonist use were quite the same in all three treatment groups. Although inhaled budesonide group resulted in significantly greater improvements compared with the other two groups in the lung function the changes in FEV₁ and PEF are within the baseline variability and there was no statistically significant difference.
Comparison of low-dose inhaled corticosteroids plus theophylline and high-dose inhaled corticosteroids

Comparison of Addition of Theophylline to Inhaled Steroid with Doubling of the Dose of Inhaled Steroid in Asthma

Summary:
Theophylline plus BDP 400 mcg/day was clinically equivalent with doubling dose of BDP (800 mcg/day) in asthmatics who remained symptoms on BDP 400mcg/day. Both treatments increased PEF and reduced PEF variability significantly, and improved asthma symptoms and rescue medication use. There were no significant differences between the treatments.
No serious adverse event was reported. Twenty seven adverse events were observed in Theophylline plus BDP group (15 gastro-intestinal symptoms, 6 palpitations, and 6 respiratory symptoms such as dyspnea or cough), and 17 events were observed in high-dose BDP group (4 gastro-intestinal symptoms, 2 palpitations, and 11 respiratory symptoms).

A Comparison of Low-dose Inhaled Budesonide Plus Theophylline and High-dose Inhaled Budesonide for Moderate Asthma.

Summary :
In 62 patients with persistent symptoms despite use of inhaled corticosteroids, both of budesonide 800 mcg/day plus theophylline and budesonide 1,600 mcg/day improved lung function. Budesonide plus theophylline treatment resulted in greater improvements in FVC and FEV₁ than high-dose budesonide only treatment. There were similar reductions in Beta-agonists use and PEF variability.
Both treatments were well tolerated. Nine patients received low-dose budesonide plus theophylline reported adverse events (gastrointestinal upset in 5 patients, palpitation in 2, sore throat in 1, and headache in 1) as did seven patients in high-dose budesonide group (sore throat in 3, gastrointestinal upset in 2 patients, rosacea in 1, palpitation in 1). There was reduction in serum cortisol concentrations in high-dose budesonide group, but not in low-dose Budesonide plus theophylline group.
Comparison of high dose inhaled steroids, low dose inhaled steroids plus low dose theophylline, and low dose inhaled steroids alone in chronic asthma in general practice.


Summary:
Asthmatic patients with continuing asthma symptoms with BDP 400 mcg/day were recruited in a study to compare low-dose theophylline plus low-dose BDP (400 mcg/day) with high-dose BDP (1,000 mcg/day). Patients in low-dose theophylline plus BDP group significantly increased evening PEF at the end of study compared with entry value, but not in high-dose steroids group.

Concerning side effects, there were no significant differences between the treatment groups for any of the commonly reported symptoms.
Add on effects of theophylline to high-dose inhaled corticosteroids

Efficacy of Uniphyl, Salbutamol, and Their Combination in Asthmatic Patients in High-dose Inhaled Steroids

Summary:
A group of 32 patients with moderately severe asthma maintained on inhaled corticosteroids 1,100 mcg/day participated in a study to assess the effect of adding theophylline, inhaled salbutamol, and their combination. Morning PEF and FEV\textsubscript{1} were significantly higher with adding theophylline alone or combination of theophylline and salbutamol than with salbutamol alone.
Side effects reported were mild to moderate severity, and the mean severity ratings did not differ between treatment groups. Three patients (one in each of Uniphyl, combination therapy, and salbutamol phases) withdrew study because of side effects.

Immunomodulation by Theophylline in Asthma.

Summary:
The effects of theophylline withdrawal in asthmatic patients treated with long-term theophylline plus high dose inhaled corticosteroids (mean dose 1548 mcg/day of BDP or budesonide). Theophylline withdrawal significantly associated with a significant increase in asthma symptoms and a fall in FEV\textsubscript{1} and morning PEF. This was accompanied by a significant fall in blood T cells and an increase in T cells in the airway.
Effects of Theophylline in COPD treatment.

Effects of Theophylline on Diaphragmatic Strength and Fatigue in Patients with Chronic Obstructive Pulmonary Disease.

Summary:
In 15 patients with severe COPD, theophylline (mean plasma level 13 mcg/mL) increased maximal transdiaphragmatic pressure by 16% after 7 days of administration, and increase persisted after 30 days. Theophylline also suppressed diaphragmatic fatigue.

The Effect of Oral Aminophylline on Lung Mucociliary Clearance in Man.

Summary:
Sustained release aminophylline caused a significant increase in tracheobronchial mucociliary clearance in 12 patients with obstructive lung disease. This acceleration occurred during the two hours following inhalation of radioaerosol.

A Comparison of Inhaled Ipratropium, Oral Theophylline Plus Inhaled β-Agonist, and the Combination of All Three in Patients With COPD.

Summary:
In 48 COPD patients, the role of inhaled ipratropium alone vs. oral theophylline plus inhaled β-agonist or the combination of all three was evaluated. The combination of theophylline and β-agonist was superior in an improvement of FEV₁ to ipratropium alone, and all three drugs together were superior to the other treatment regimen.
Effects of theophylline and ipratropium bromide on exercise performance in patients with stable chronic obstructive pulmonary disease.


Summary:
Theophylline, ipratropium, combination of both drugs and placebo were studied in COPD patients. Theophylline and ipratropium produced greater increases in FEV₁, maximal oxygen consumption, and several dyspnea ratios than placebo. A combination of both drugs produced greater improvements in pulmonary function and exercise capacity than either drug alone.

Salmeterol Plus Theophylline Combination Therapy in the Treatment of COPD.


Summary:
COPD patients randomly assigned to received salmeterol plus theophylline, salmeterol, or theophylline for 12 weeks. Combination treatment with salmeterol plus theophylline significantly provided greater improvements in pulmonary function; decreases in symptoms dyspnea and albuterol use; and significantly fewer COPD exacerbations.

The Efficacy of Orally Administered Theophylline, Inhaled Salbutamol, and a Combination of the Two as Chronic Therapy in the Management of Chronic Bronchitis with Reversible Air-Flow Obstruction.


Summary:
COPD patients received sustained-release theophylline, inhaled salbutamol, combination of the 2 drugs, and placebo. Improvements in FEV₁ and FVC were a consistent finding with combined group compared with placebo.
Bronchodilators in Chronic Air-Flow Limitation - Effects on Airway Function, Exercise Capacity, and Quality of Life.


Summary:
COPD patients underwent 4 treatment periods during which they received placebo-placebo, placebo-salbutamol, placebo-theophylline, and salbutamol-theophylline. Clinically important and statistically significant differences between the 4 periods were noted on both physiologic and functional outcomes. For the group as a whole, improvement with salbutamol and theophylline was comparable, and additional benefit was gained from a combination of the 2 drugs.

Value of theophylline treatment in patients handicapped by chronic obstructive lung disease.


Summary:
This trial was designed to test whether the addition of prescribed theophylline would produce any additional advantage in spirometric or functional variables in COPD patients. Improvements in PEF, trapped gas volumes, two stage vital capacity, distances walked, breathlessness in everyday activities, and fatigue were found at serum theophylline concentration 17 mcg/mL.
A randomized, controlled trial of theophylline in patients with severe chronic obstructive pulmonary disease.


Summary:
To assess the effects of theophylline in COPD, patients were studied before and after two months of placebo and two months of treatment with theophylline. After taking theophylline for two months (mean plasma concentration, 14.8 mcg/mL), as compared with placebo, the patients had significant improvements in dyspnea, pulmonary gas exchange, partial pressure of arterial carbon dioxide, VC and FEV1. Minute ventilation increased in the patients taking theophylline because of increased tidal volume, with no change in respiratory frequency. The respiratory-muscle performance of the patients taking theophylline improved.

Effect of theophylline on induced sputum inflammatory indices and neutrophil chemotaxis in chronic obstructive pulmonary disease.


Summary:
Twenty-five patients with COPD were treated with theophylline (plasma level of 9-11 mg/L) for 4 weeks. Induced sputum inflammatory cells, neutrophils, interleukin-8, myeloperoxidase, and lactoferrin were all significantly reduced by about 22% by theophylline. Neutrophils from subjects treated with theophylline showed reduced chemotaxis to N-formyl-met-leu-phe (approximately 28%) and interleukin-8 (approximately 60%). These results suggest that theophylline has antiinflammatory properties that may be useful in the long-term treatment of COPD.
9. Summary of comparative evidence on safety:

**Adverse reactions of theophylline**

Theophylline is known to develop adverse reactions in a blood concentration-dependent fashion. Adverse reactions are frequently observed with patients who receive theophylline $\geq 20 \, \mu g/mL$. Therefore, there are many reports which have stated that the upper limit for therapeutic dose range is $20 \, \mu g/mL$. In recent years, however, there are many data reporting theophylline 5-15 $\mu g/mL$.

Weinberger et al. investigated the incidences of theophylline adverse reactions in 404 patients who were on treatment at Iowa University. Consequently, they demonstrated that the incidences are low at a blood theophylline concentration of $\leq 20 \, \mu g/mL^{75}$.

<table>
<thead>
<tr>
<th>Serum concentration ($\mu g/mL$)</th>
<th>Incidence of adverse effects (no. subjects affected/no. subjects studied [%])</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Children</td>
</tr>
<tr>
<td>$&lt; 10$</td>
<td>0/29</td>
</tr>
<tr>
<td>10-19.9</td>
<td>5/258 (2)</td>
</tr>
<tr>
<td>$\geq 20$</td>
<td>17/61 (28)</td>
</tr>
</tbody>
</table>

Data were obtained by questioning patients at the time when the initial blood sample was collected in sequentially selected ambulatory patients whose dose had been titrated over 9 days.

In addition, the fact that no serious adverse reactions developed in large-scale, double-blind
studies of theophylline in recent years indicate that theophylline has no safety concern when used under full control. Furthermore, Derby et al. have reported in a follow-up study in 35,909 outpatients that the incidence of xanthine intoxication was 7.8/10,000 persons/year and that hospitalization due to xanthine intoxication was relatively rare. A survey on the safety of theophylline in Japan investigated for 1 month all patients who started to receive or were receiving theophylline at study institutions, found adverse reactions in 54 (1.38%) of 3,909 patients and discovered no serious adverse reactions. This result indicates that theophylline involves no safety problem when used properly.

Theophylline provokes seizures as a serious adverse reaction. Many of the reports which described seizures stated blood theophylline concentrations of > 20 µg/mL. On the other hand, there are a few reports which described that convulsive disease is related with theophylline also at a blood theophylline concentration which is equivalent to or below the efficacy range. Dunn et al. have reported a decrease in blood antiepileptic drug concentration and the presence of febrile disease in pediatric patients with seizures of status epilepticus who received theophylline at a dose below the efficacy range. Bahl et al. have mentioned a 78-year-old patient who developed seizures; the patient previously used phenytoin for suspected tonic seizures. Theophylline should not be considered to be a drug of first choice for such patients with a risk factor of seizures and it is necessary to exercise caution to the dose of theophylline at the time of its administration to such patients.

A retrospective survey by pediatricians has indicated that the incidence of seizures in pediatric patients with asthma who were receiving theophylline was 0.24% (127/54,066) and was 0.36% (27/7,568) in pediatric patients with asthma who were not receiving theophylline. Furthermore, as stated in Clause “1. Pharmacological actions of theophylline”, theophylline has been found to exercise anti-inflammatory activity also at low serum concentration. Therefore, theophylline has come to be in use at a safer dose.

REFERENCE
79) Derby LE et al.: Hospital Admission for Xanthine Toxicity. Pharmacotherapy 10(2), 112-
114, 1990


10. **Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group:**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Defined Daily Dose</th>
<th>Price</th>
<th>Price per Daily Dose</th>
</tr>
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<td>Theophylline</td>
<td>400mg</td>
<td>0.0059 (200mg)</td>
<td>0.0118</td>
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<tr>
<td>Ipratropium Bromide</td>
<td>0.12mg</td>
<td>0.005–0.181 (250mcg/1ml)</td>
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<td>Salbutamol (Respol)</td>
<td>10mg</td>
<td>0.0028–0.131 (5mg/ml)</td>
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<tr>
<td>Salbutamol (Inhaler)</td>
<td>0.8mg</td>
<td>0.0095–0.0135 (0.1mg/Dose)</td>
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<td>Beclometasone (Inhaler)</td>
<td>0.8mg</td>
<td>0.0100–0.0191 (50mcg/Dose)</td>
<td>0.1600–0.3056</td>
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Table 1: Cost of daily dose (Data from the International Drug Price Indicator Guide)
### Application for the Inclusion of Theophylline in the WHO Model List of Essential Medicines

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

Theophylline is now available as follows:

<table>
<thead>
<tr>
<th>Originator</th>
<th>Licensee</th>
<th>Generics Name</th>
<th>World Status</th>
<th>Drug Name</th>
<th>Country Data</th>
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<td>Launched</td>
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<td>Formulation, optimized, extended-release, Formulation, modified-release, immediate</td>
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Application for the Inclusion of Theophylline in the WHO Model List of Essential Medicines

<table>
<thead>
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## Application for the Inclusion of Theophylline in the WHO Model List of Essential Medicines

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## Application for the Inclusion of Theophylline in the WHO Model List of Essential Medicines

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<td>Argentina Registered Australia Pre-registration Austria Launched 1983 Belgium Registered Brazil Registered France Registered Germany Launched 1988 Greece Registered Ireland Registered Israel Pre-registration Italy Launched 1995 Japan Phase II Clinical Trial Mexico Registered Netherlands Launched 1993 New Zealand Pre-registration Peru Pre-registration Philippines Pre-registration Portugal Registered South Africa Launched 1995 South Korea Pre-registration Spain Launched 1992 Sweden Registered Switzerland Launched 1993 UK Registered USA Pre-registration</td>
<td>Formulation, modified-release, C≤24hr Antisthma</td>
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<td>Formulation, modified-release, other</td>
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<td>Formulation, modified-release, other</td>
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<td>Theclong</td>
<td>Japan Launched 1997</td>
<td>Formulation, modified-release, other Antisthma</td>
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</table>

British Pharmacopoeia: Available
International Pharmacopoeia: no
United States Pharmacopoeia: Available

(For reference: Japanese Pharmacopoeia: Available)
13. Proposed (new/adapted) text for the WHO Model Formulary

**Theophylline and Aminophylline**

Aminophylline is a representative xanthine bronchodilator. Various drugs including theophylline can serve as alternatives

**Tablets**, theophylline 100 mg

**Modified-release tablets**, theophylline 200 mg, 300 mg

**Injection** (Solution for injection), aminophylline 25 mg/ml, 10-ml ampoule

**Uses:**
chronic asthma including nocturnal asthma; acute severe asthma

**Contraindications:**
porphyria; known hypersensitivity to ethylenediamine (for aminophylline)

**Precautions:**
cardiac disease, hypertension, hyperthyroidism, peptic ulcer, epilepsy, hepatic impairment (Appendix 5), pregnancy (Appendix 2), breastfeeding (Appendix 3), elderly, fever; smokers may require larger or more frequent doses; **interactions**: Appendix 1

**Dosage:**
Chronic asthma, **by mouth** (as tablets), **ADULT** and **CHILD** over 12 years, 100–200 mg 3–4 times daily after food; **by mouth** (as modified-release tablets) **ADULT** 300–450 mg every 12 hours

Nocturnal asthma, **by mouth** (as modified-release tablets), **ADULT** total daily requirement as single evening dose

*Note.* Plasma theophylline concentration for optimum response 10–20 mg/litre (55–110 micromol/litre); narrow margin between therapeutic and toxic dose; see notes above; a range of 5–15 mg/litre (27.5–82.5 micromol/litre) may be effective and associated with fewer adverse effects

Acute severe asthma (**not** previously treated with theophylline), **by slow intravenous injection** (over at least 20 minutes), **ADULT** and **CHILD** 5 mg/kg; maintenance, **by intravenous infusion**, **ADULT** 500 micrograms/kg/hour; **CHILD** 6 months–9 years, 1 mg/kg/hour, 10–16 years, 800 micrograms/kg/hour, adjusted according to plasma-theophylline concentration

*Note.* Patients taking oral theophylline (or aminophylline) should not normally receive intravenous aminophylline unless plasma-theophylline concentration is available to guide dosage

**Adverse effects:**
nausea and other gastrointestinal disturbances, restlessness, anxiety, tremor, palpitations, headache, insomnia, dizziness; convulsions, arrhythmias and hypotension—especially if given by rapid injection; urticaria, erythema and exfoliative dermatitis—resulting from hypersensitivity to ethylenediamine component of aminophylline