Application for the Inclusion of Cromoglicic acid in the WHO Model List of Essential Medicines

SUBMITTED BY:
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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

We hereby request that cromoglicic acid (disodium chromoglycate,DSCG), which is included in the WHO Model List but is shown to be one of the drugs to be deleted, continue to be included in the list.

The reasons are as follows.

a. The drug’s usefulness has been confirmed in pediatric asthma (improvement of subjective symptoms by a systematic review).

b. Many randomized controlled trials (RCTs) have confirmed improvements in symptoms and respiratory function in adult asthma as well.

c. The drug’s usefulness has been confirmed (by two systematic reviews) in exercise-induced asthma (EIA).

d. High-level safety, especially in long-term use, in infants and pregnant women, has been confirmed (observational data).

e. Financial burden is alleviated through reduction in the number of hospital stays, etc. (retrospective research).

The above assertions are supported by strong clinical evidence. Moreover, the Global Initiative for Asthma (GINA) 2002, which are currently the most widely accepted guidelines for asthma prevention and management, as well as the Japanese and US national guidelines, recommend the use of this drug because of its high degree of usefulness. We therefore feel it appropriate and justifiable to continue to have the drug included in this list.

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)
   JSA (Japanese Society of Allergology)
   JSPA (Japanese Society of Pediatric Allergy and Clinical Immunology)

4. International Nonproprietary Name (INN, generic name) of the medicine
cromoglicic acid (WHO recommended INN)

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

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

   Overseas, prevalence of childhood asthma ranges from 0% to 30% depending
   on the country. The rate is especially high in Australia, New Zealand and the
   UK (Cited from Figure 2-1, 2-2; GINA GL).
   In Japan, cumulative prevalence of asthma according to ATS-DLD (American
   Thoracic Society Division of Lung Diseases) is 5.1% in infants, 6.4% in
   children, and 3.2% in adults (about 6.2% for ages 15 to 30). Meanwhile, an
   ISAAC (International Study of Asthma and Allergies in Childhood) survey
   targeting ages 13 to 14 showed that prevalence was 13% and 19%,
   respectively, in Fukuoka and Tochigi Prefectures.
   The prevalence of asthma itself is sharply on the rise. Three chronological
   surveys are available in Japan, implemented by the same physician using the
   same protocol and selecting subjects from the same environmental
   backgrounds. These surveys confirm that the prevalence of asthma has been
   increasing at a rate of about 1.5- to 2-fold every ten years or so. A similar
trend is seen in other countries. This has also been confirmed by two surveys,
implemented after an interval of over 9 years, using the same method (Figures
2-3).
<table>
<thead>
<tr>
<th></th>
<th>'70</th>
<th>'80</th>
<th>'90</th>
<th>Survey targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kita-Kyushu</td>
<td>1.6% (71)</td>
<td>3.6% (81)</td>
<td>5.4% (91)</td>
<td>6-12y (*1)</td>
</tr>
<tr>
<td>Oslo</td>
<td>2.2% (81)</td>
<td>4.2% (93)</td>
<td></td>
<td>School children (*2)</td>
</tr>
<tr>
<td>South Wales</td>
<td>17% (73) 6%</td>
<td>22% (88) 12%</td>
<td></td>
<td>7y (*3) (*4)</td>
</tr>
<tr>
<td>Australia</td>
<td>21% (87) 5.6% (87)</td>
<td>22% (88) 8% (90)</td>
<td></td>
<td>Adults (*3) (*5)</td>
</tr>
</tbody>
</table>

*1: current asthma (ATS-DLD)  *2: current asthma (Diagnosed asthma)  *3: wheezing  *4: cumulative asthma (Diagnosed asthma)  *5: current asthma
### Figure 2.1. Prevalence of Asthma in Children

<table>
<thead>
<tr>
<th>Country</th>
<th>Study year</th>
<th>N (m)</th>
<th>Age</th>
<th>Current asthma</th>
<th>Diagnosed asthma</th>
<th>Atopy (SPT)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>82</td>
<td>1,437</td>
<td>8-10</td>
<td>3.4</td>
<td>11.1</td>
<td>21.7</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>85</td>
<td>1,317</td>
<td>8-11</td>
<td>3.7</td>
<td>17.3</td>
<td>25.6</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>91-92</td>
<td>6,351</td>
<td>8-11</td>
<td>10.3</td>
<td>35.2</td>
<td>24.2</td>
<td>15</td>
</tr>
<tr>
<td>Australian Aboriginal</td>
<td>51</td>
<td>215</td>
<td>7-12</td>
<td>0.1</td>
<td>0.4</td>
<td>2.0(9)</td>
<td>20</td>
</tr>
<tr>
<td>New Zealand</td>
<td>81</td>
<td>813</td>
<td>6-11</td>
<td>1.1</td>
<td>0.1</td>
<td>10.0</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>89</td>
<td>878</td>
<td>6-11</td>
<td></td>
<td></td>
<td>0.8</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>670</td>
<td>6-11</td>
<td></td>
<td></td>
<td>16.0</td>
<td>19</td>
</tr>
<tr>
<td>England</td>
<td>86</td>
<td>947</td>
<td>6-11</td>
<td></td>
<td></td>
<td>10.0</td>
<td>21</td>
</tr>
<tr>
<td>Germany</td>
<td>86-88</td>
<td>1,897</td>
<td>9-11</td>
<td>11.1</td>
<td>14.2</td>
<td>23.0(91)</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>89-90</td>
<td>758</td>
<td>9-11</td>
<td>14.0</td>
<td>16.6</td>
<td>20.0(92)</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>89-90</td>
<td>1,207</td>
<td>9-11</td>
<td>14.0</td>
<td>16.6</td>
<td>20.0(92)</td>
<td>23</td>
</tr>
<tr>
<td>Denmark</td>
<td>86-88</td>
<td>744</td>
<td>6-10</td>
<td>0.6</td>
<td>5.9</td>
<td>8.4(9)</td>
<td>34</td>
</tr>
<tr>
<td>Japan</td>
<td>86-88</td>
<td>2,246</td>
<td>13-14</td>
<td>4.0</td>
<td>11.0</td>
<td>14.0(91)</td>
<td>35</td>
</tr>
<tr>
<td>China (Han)</td>
<td>82</td>
<td>917</td>
<td>12-20</td>
<td>1.1</td>
<td>4.1</td>
<td>15.0</td>
<td>27</td>
</tr>
<tr>
<td>Kenya</td>
<td>91</td>
<td>412</td>
<td>9-12</td>
<td>0.3</td>
<td>11.4</td>
<td>10.7(91)</td>
<td>28</td>
</tr>
<tr>
<td>Australia</td>
<td>86</td>
<td>531</td>
<td>12-15</td>
<td>11.4</td>
<td>14.0</td>
<td>14.0(91)</td>
<td>29</td>
</tr>
<tr>
<td>US (Texas)</td>
<td>86-87</td>
<td>716</td>
<td>6</td>
<td>26.8</td>
<td>40.0</td>
<td>40.0(92)</td>
<td>30</td>
</tr>
</tbody>
</table>

*Data are illustrative of the variation of childhood asthma prevalence and not a comprehensive list.

Current asthma: at least one symptom**.

Diagnosed asthma: currently diagnosed***.

Atopy (SPT): skin prick test.

** Any wheeze in the last 12 months.
*** Skin prick test: ** more than 2 mm wheal, *** more than 15 mm.
Childhood asthma often develops in infancy, while adult asthma develops more or less equally in all age groups. Frequency of onset is slightly higher between the ages of 20 and 39.
Deaths due to asthma have been decreasing steadily in recent years. In 2001, the mortality rate of asthma per 100,000 people was 3.2 (3.4 in men and 3.0 in women). This rate was the lowest ever recorded in Japan.

A comparison of the mortality rate of asthma by age group between 1979 and 2001 revealed that men between the ages of 20 and 29 showed a slower decrease in asthma-associated mortality rate than other age groups. Moreover, mild and moderate-degree patients are accounting for a growing proportion of total asthma-related fatalities in both children and adults in recent years. Still, many patients suffer fatal attacks following a stormy course.

At present, DSCG (disodium Chromoglycate) is primarily administered to children in Japan. Inhalant liquid is the most commonly used dosage form.

The number of patients taking DSCG (monthly average), as estimated from the 2003 sales value in Japan, is approximately 90,000 for inhalant liquids, approximately 20,000 for aerosol, and approximately 4,000 for capsules.

Reference:
2) Nishima S et al. Arerugi 1993;42:192-204

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

a. Global Initiative for Asthma 2003

   Adults and children: Mild persistent types: DSCG may be used as a
controller optionally.

DSCG can be given prophylactically to inhibit allergen-induced airflow limitation, and acute airflow limitation after exposure to exercise, cold dry air and sulfur dioxide.

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**Figure 7-8. Recommended Medications by Level of Severity: Children**

<table>
<thead>
<tr>
<th>Level of Severity**</th>
<th>Daily Controller Medications</th>
<th>Other Treatment Options***</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong> Intermittent Asthma****</td>
<td>• None necessary</td>
<td></td>
</tr>
</tbody>
</table>
| **Step 2** Mild Persistent Asthma | • Inhaled glucocorticosteroid (100-400 µg budesonide or equivalent) | • Sustained-release theophylline, or  
  • Cromone, or  
  • Leukotriene modifier |
| **Step 3** Moderate Persistent Asthma | • Inhaled glucocorticosteroid (400-600 µg budesonide or equivalent) | • Inhaled glucocorticosteroid (< 800 µg budesonide or equivalent)  
  plus sustained-release theophylline, or  
  • Inhaled glucocorticosteroid (< 800 µg budesonide or equivalent)  
  plus long-acting inhaled β₂-agonist, or  
  • Inhaled glucocorticosteroid at higher doses (> 800 µg budesonide or equivalent), or  
  • Inhaled glucocorticosteroid (> 800 µg budesonide or equivalent)  
  plus leukotriene modifier |
| **Step 4** Severe Persistent Asthma | • Inhaled glucocorticosteroid (> 800 µg budesonide or equivalent) plus one or more of the following, if needed:  
  • Sustained-release theophylline  
  • Long-acting inhaled β₂-agonist  
  • Leukotriene modifier  
  • Oral glucocorticosteroid | |

All Steps: Once control of asthma is achieved and maintained for at least 3 months, a gradual reduction of the 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.

**See Figure 5-6 and Figure 5-7 for classification of severity.

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

****Children with intermittent asthma but severe exacerbations should be treated as having moderate persistent asthma (Evidence D).
### Figure 7-5. Recommended Medications by Level of Severity: Adults

**All Steps:** 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.

<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 Asthma</td>
<td>• Inhaled glucocorticosteroid (≤ 500 μg BDP or equivalent)</td>
<td>• Sustained-release theophylline, or&lt;br&gt;• Cromone, or&lt;br&gt;• Leukotriene modifier</td>
</tr>
<tr>
<td>Step 3 Moderate Persistent Asthma</td>
<td>• Inhaled glucocorticosteroid (200-1,000 μg BDP or equivalent) plus long-acting inhaled β2-agonist</td>
<td>• Inhaled glucocorticosteroid (500-1,000 μg BDP or equivalent) plus sustained-release theophylline, or&lt;br&gt;• Inhaled glucocorticosteroid (500-1,000 μg BDP or equivalent) plus long-acting oral β2-agonist, or&lt;br&gt;• Inhaled glucocorticosteroid at higher doses (&gt; 1,000 μg BDP or equivalent), or&lt;br&gt;• Inhaled glucocorticosteroid (500-1,000 μg BDP or equivalent) plus leukotriene modifier</td>
</tr>
<tr>
<td>Step 4 Severe Persistent Asthma</td>
<td>• Inhaled glucocorticosteroid (&gt; 1,000 μg BDP or equivalent) plus long-acting inhaled β2-agonist, plus one or more of the following, if needed:&lt;br&gt;• Sustained-release theophylline&lt;br&gt;• Leukotriene modifier&lt;br&gt;• Long-acting oral β2-agonist&lt;br&gt;• Oral glucocorticosteroid</td>
<td></td>
</tr>
</tbody>
</table>

**All Steps:** Once control of asthma is achieved and maintained for at least 3 months, a gradual reduction of the 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.

** See Figure 5.6 and Figure 5.7 for classification of severity.

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

**** Those with intermittent asthma but severe exacerbations should be treated as having moderate persistent asthma (Evidence D).
· Over 5 years of age: Mild persistent types: Along with low-dose steroid inhalants (200-400 µg if converted to BDP-CFC equivalent), anti-inflammatory drugs may be used optionally.
· 5 years or under: Mild persistent types: Use of the drug for anti-inflammatory purposes is recommended (use of a nebulizer is recommended).

<table>
<thead>
<tr>
<th>DSCG drug form</th>
<th>Adult dosage</th>
<th>Pediatric dosage</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDI (1 mg)</td>
<td>2-4 puffs 3-4 times a day</td>
<td>1-2 puffs 3-4 times a day</td>
<td>A dose prior to exercise and antigen exposure shows preventive effects lasting 1-2 hours</td>
</tr>
<tr>
<td>Inhalant liquid (20 mg)</td>
<td>1A per dose, 3-4 times a day</td>
<td>1A per dose, 3-4 times a day</td>
<td></td>
</tr>
</tbody>
</table>

c. Japanese Guidelines (children/adults)

Adults: Mild intermittent types: Consider using the drug as needed. (If EIA develops, ensure that the patients inhale the drug prior to exercise.)
Mild persistent types: Low-dose steroid inhalants (200-400 µg if converted to BDP-CFC equivalent) may be used optionally.
· Administer a dose of 20 mg (in capsule or inhalant liquid form) 3 to 4 times a day
(Dose of aerosol: 2 mg).
To assess efficacy in individual patients, the drug must be administered for more than 4 to 6 weeks.

Children: Mild intermittent types: Consider using the drug as needed. (If EIA develops, ensure that the patients inhale the drug prior to exercise.)

Mild persistent types: For ages 6 to 15, minimum-dose steroid inhalants (200 µg or less if converted to BDP-CFC equivalent) may be used optionally.
For ages 2 to 5, consider using concomitant oral antiallergic drugs in combination with \(\beta_2\) stimulants (twice a day); for patients
under 2 years of age, in combination with $\beta_2$ stimulants as needed.

Moderate persistent types: For ages 6 to 15, consider using concomitant low-dose steroid inhalants (200-400 µg if converted to BDP-CFC equivalent) as needed.

For ages 2 to 5, consider using low-dose steroid inhalants (200-300 µg if converted to BDP-CFC equivalent); for under 2 years of age, concomitant minimum-dose steroid inhalants (200 µg or less if converted to BDP-CFC equivalent) in combination with $\beta_2$ stimulants (three times a day) as needed.

Severe persistent types: For ages 6 to 15, use concomitant moderate-dose steroid inhalants (400-800 µg if converted to BDP-CFC equivalent).

For ages 2 to 5, use concomitant low-dose steroid inhalants (300-600 µg if converted to BDP-CFC equivalent); for under 2 years of age, concomitant low-dose steroid inhalants (300-400 µg if converted to BDP-CFC equivalent) in combination with $\beta_2$ stimulants (four times a day).

- Administer a dose of 20 mg (in capsule or inhalant liquid form) 2 to 4 times a day (Dose of aerosol: 2 mg).

Reference:


8. 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

a. Childhood asthma

We conducted a search using Pub Med (MeSH words: cromolyn sodium, child, asthma, randomized controlled trials) (1966-2004).

There were 118 hits altogether, 3 of which pertained to systematic reviews. (There were 53 hits if narrowed down to “clinical trials.”)

(1) “Inhaled disodium cromoglycate as maintenance therapy in children with asthma: a systematic review”

(2) “Sodium cromoglycate in childhood asthma”

(2)’ “Inhaled sodium cromoglycate in children with asthma”

(3) “Inhaled sodium cromoglycate for asthma in children”
(4) “Inhaled sodium cromoglycate for asthma in children” (critique)

(www.update-software.com/ccng/ccng.exe?SourceID=CD002173)

Of these, (2) is a rebuttal to (1). Authors of (1) stated that DSCG and a placebo showed no differences in their effects of improving coughing and wheezing symptoms in pediatric asthma patients. However, of the 24 reports taken up originally, 19 showed positive results. Authors of (2) insisted that there were problems with the trials taken up in (1), explaining that some trials should have been included but others should have not. They also saw problems in the validity of the tolerance interval. Results of analysis recalculated from these perspectives are presented in (2)', with the authors concluding that DSCG has sufficient therapeutic effects, and that the effects are markedly higher in school-age children than in younger children.

(4) is also a rebuttal to (3). The summary of criticism (4) is as follows.

- 24 trails was analyzed in the review, but the primary endpoint of this analysis was “symptom-free days” which was reported as the primary outcome only in 4 of 24 trials included in this review.

In addition, cromolyn was likely to be dominant to placebo on this end point though it’s not significant.

- On the secondary end points, cromolyn was dominant in 8 of 16 items.

There was no trials which reported placebo was dominant to cromolyn. Since no valid rebuttals exist to the above rebuttals (conclusion), and since there are many other reports in Japan and other countries that describe the usefulness of DSCG, we support the usefulness of DSCG in pediatric asthma.

Similarly, regarding severe cases, randomized controlled trials exist: a search using Pub Med (1966-2002) produced 9 pertinent reports, 2 of which were reports on inhalant liquids. Of these, a report by Furusho et al. (DSCG + small-dose β2; timed inhalation therapy) provides grounds for

Infants in particular often have difficulty in mastering the inhalation technique. In this case, therefore, inhalation via nebulizer is considered an important treatment method.

Combining DSCG with inhalation of small-dose $\beta_2$ agonist is a therapeutic method unique to Japan. Nishikawa et al. confirmed that this therapy helped improve symptoms and clearly decreased the number of inpatients (Iryo: 44(7), 1990).

Japanese guidelines for pediatric asthma recommend this therapy as a highly effective treatment for use in infants with mild asthma, or in children with moderate or severe asthma (to be used in combination with inhalant steroids).

Reference:
20) Hyde JS et al. Short- and longterm prophylaxis with cromolyn sodium in chronic asthma. Chest 1973;63:875-880

31) Bertelsen A et al. Nebulised sodium cromoglycate in the treatment of wheezy bronchitis. Allergy 1986;41:266-270
33) Bernard A et al. Cromolyn sodium in the treatment of children with


b. Adult asthma

We conducted a search using Pub Med (MeSH words: cromolyn sodium, asthma, adult, randomized controlled trials, placebo) (1966-2004). There were 147 hits altogether. However, none pertained to systematic review. If the above were narrowed down to “clinical trials,” 95 reports were confirmed. The contents of these reports are summarized below.

- Improvement of subjective symptoms
  Many reports have confirmed the usefulness of DSCG in terms of asthmatic symptom improvement effects, the most important index in asthma treatment (Blumenthal et al.; JACI, 1998, and others).

- Improvement of respiratory function
  Like above, many reports state that the drug showed improvement effects (Furukawa et al.; JACI, 1998, and others).

- Improvement of airway hypersensitivity
  Regarding airway hypersensitivity, currently there are both positive and negative reports.
  According to the latest report (Lindqvist et al.; JACI, 2003), DSCG showed improvement effects similar to those of fluticasone.

- Anti-inflammatory activity
  Like above, there are both positive and negative reports. Again, according to the latest report (Lindqvist et al.; JACI, 2003), unlike the placebo (salmeterol), DSCG had effects comparable to those of fluticasone.
For the above reasons, we support the usefulness of DSCG in adult asthma, as in pediatric asthma. Japanese guidelines also recommend use of the drug in patients with mild persistent asthma.

Reference:


40) Blumenthal MN et al. Evaluation of a non-chlorofluorocarbon formulation of cromolyn sodium (Intal) metered-dose inhaler versus the chlorofluorocarbon formulation in the treatment of adult patients with asthma: a controlled trial.


43) Carrasco E et al. Comparison of 1 mg and 5 mg sodium cromoglycate
metered dose inhalers in the treatment of asthma: a 12-week double-blind, parallel group trial.


45) Eigen H et al. Evaluation of the addition of cromolyn sodium to bronchodilator maintenance therapy in the long-term management of asthma.


47) Diaz P et al. Bronchoalveolar lavage in asthma: the effect of disodium cromoglycate (cromolyn) on leukocyte counts, immunoglobulins, and complement.


c. Exercise Induced Asthma (EIA)

A search was conducted using Pub Med (MeSH words: cromolyn sodium, asthma exercise-induced, randomized controlled trials, placebo) (1966-2004).

There were 28 hits altogether, 28 of which were reports on trials of DSCG. Of these, the following two reports were systematic reviews registered with the Cochrane library.

(1) “Mast-cell stabilizing agents to prevent exercise-induced
bronchoconstriction”  
Spooner CH, Spooner GR, Rowe BH  
(2) “Nedocromil sodium and sodium cromoglycate for preventing exercise-induced bronchoconstriction”  
Kelly K, Spooner CH, Rowe BH  

Of these, (2) states that DSCG has effects comparable to nedocromil. The effects of DSCG against EIA are investigated in (1). This report states as follows:  
- DSCG, like anti-cholinergic drugs, clearly suppressed the reduction of post-exercise pulmonary function, and its effects were significantly superior to anti-cholinergic drugs.  
- However, these effects were inferior to those of SABA.  
- As far as existing data are concerned, there is no evidence that shows the effects of SABA + DSCG being superior to SABA monotherapy.  

Twenty-eight reports that had been searched as above confirmed the efficacy of DSCG, so we believe that DSCG is definitely useful for EIA.  

Reference:  
56) Ahmed T et al. Preventing bronchoconstriction in exercise-induced asthma


9. 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

A search was conducted using Pub Med (MeSH words: cromolyn sodium, asthma, safety, long-term or infant or pregnancy) (1966-2004).
There were 4 hits for “long-term,” 3 for “infant,” and 3 for “pregnancy.”
Those that focus especially on DSCG are shown below, along with a summary of their contents.

a. Long-term (Multi-centre surveillance of long-term safety of sodium cromoglycate;

This is a report on a multicenter study of DSCG conducted after its release in the US market, in response to a request by the FDA. According to this report, continuous inhalation of DSCG induced no abnormalities in the X-ray images (for 5 years) or in any of the parameters in pulmonary function tests (for 4 years) or immunological blood tests (2 to 4 years).

b. Infants (Nebulized cromoglycate, theophylline, and placebo in preschool asthmatic children. (Glass J.: Arch. Dis. Child. 56(8): 648-51, 1981, etc.) Although there are no reports that focus on safety of DSCG in this age group, a number of reports on RCTs involving placebo discuss the issue of safety.

No serious cases were found in any of these reports, and we believe that there are no major problems in terms of safety (tolerability) in infants.

c. Pregnancy (The efficacy and safety of asthma medications during pregnancy;

Schatz M. Semin Perinatol. 25(3): 145-152 (review), 2001)

There are three reports on administration of DSCG in pregnant women. Wilson (Acta Ther (8) 45-51, 1982) reported that congenital abnormality occurred in 1.4% of 296 pregnant women, while a report on the Michigan State Medicaid study entitled “Drugs in pregnancy and lactation (edition 4)” showed that the relative risk ratio confirmed by 191 pregnant women was 0.9. Furthermore, Kaiser et al. (JACI 100: 301-306, 1997) reported that administration of DSCG carried no risks of reinforcing or aggravating adverse reactions in 243 pregnant women.

Since many reports other than the above also confirmed the safety of DSCG, we believe that DSCG has a high level of safety.

Reference:

10. Summary of available data on comparative cost\(^1\) 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)

a. Drug prices in Japan are officially fixed. They are as follows:

- DSCG 20 mg 1 capsule 53.1 yen
- DSCG 20 mg 1 ampoule 76.8 yen
- DSCG aerosol (1 mg/1 puff) 3677.30 yen (200 puffs)
b. No pharmaco-economic study of this drug, based on prospective and randomized controlled trials, has been conducted in Japan. However, as mentioned above (8.b), a combination of DSCG and a small-dose $\beta_2$ inhalation is effective, especially in severe and refractory pediatric asthma patients (Pediatr Allergy Immunol 13(3): 209-216, 2002). A case report has been published in Japan that shows the correlation between the reduction in the number of seizures/hospital stays brought about by this treatment and economic efficiency (Fujii et al.; Shonika Rinsho 48(11), 1995). As a result of performing the DSCG + small-dose $\beta_2$ inhalation therapy in pediatric asthma patients (8 moderate patients and 5 severe patients) for one year, all 13 patients saw a reduction in the number of emergency visits (twice per month) and in the duration of hospital stay (a 1-night, 2-day stay).

This corresponds to approximately 30,000 yen per month and 360,000 yen per year. On the other hand, costs for regular outpatient treatment, including drug fees, are about 20,000 yen per month. The authors therefore conclude that this treatment brings about a cost benefit worth 120,000 yen per year. (Table 1 in attached file)

According to a report by Nishikawa et al. (Iryo 44(7), 1990), this therapy decreased the number of nighttime emergency visits necessitated by seizures as well as the number of seizure-induced hospitalizations to one-third, and eliminated major seizures and status epilepticus in pediatric asthma patients being hospitalized for extended periods. The amount of steroid use was decreased to one-tenth. (Table 2-5 in attached file)

Similar reports have been released in countries other than Japan. In one of them, a group of subjects receiving a drug therapy containing DSCG saw a dramatic decrease in the number of emergency visits and/or hospitalizations compared with a group of subjects receiving a drug therapy not containing DSCG. The authors concluded that a drug therapy containing DSCG was cost-effective (Ross N et al., Clin Ther 10(2): 188-203, 1988).

No studies have been carried out from the perspective of the correlation
between cost and QOL.

Reference:

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

*Source: Previously-cited NIH Guidelines

<table>
<thead>
<tr>
<th>DSCG drug form</th>
<th>Adult dosage</th>
<th>Pediatric dosage</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDI (1 mg)</td>
<td>2-4 puffs 3-4 times a day</td>
<td>1-2 puffs 3-4 times a day</td>
<td>A dose prior to exercise and antigen exposure shows preventive effects lasting 1-2 hours</td>
</tr>
</tbody>
</table>

*Source: Previously-cited JGL and JPGL

Japanese guidelines position DSCG as follows.

Adults: Mild intermittent types: Consider using the drug as needed. (If EIA develops, ensure that the patients inhale the drug prior to exercise.)
Mild persistent types: Low-dose steroid inhalants (200-400 µg if converted to BDP-CFC equivalent) may be used optionally.
Children:  
Mild intermittent types: Consider using the drug as needed. (If EIA develops, ensure that the patients inhale the drug prior to exercise.)

Mild persistent types: For ages 6 to 15, minimum-dose steroid inhalants (200 µg or less if converted to BDP-CFC equivalent) may be used optionally.

For ages 2 to 5, consider using concomitant oral antiallergic drugs in combination with $\beta_2$ stimulants (twice a day); for under 2 years of age, in combination with $\beta_2$ stimulants as needed.

Moderate persistent types: For ages 6 to 15, consider using concomitant low-dose steroid inhalants (200-400 µg if converted to BDP-CFC equivalent) as needed.

For ages 2 to 5, consider using concomitant low-dose steroid inhalants (200-300 µg if converted to BDP-CFC equivalent); for under 2 years of age, concomitant minimum-dose steroid inhalants (200 µg or less if converted to BDP-CFC equivalent) in combination with $\beta_2$ stimulants (twice a day) as needed.

Severe persistent types: For ages 6 to 15, use concomitant moderate-dose (400-800 µg if converted to BDP-CFC equivalent) steroid inhalants.

For ages 2 to 5, use concomitant low-dose steroid inhalants (300-600 µg if converted to BDP-CFC equivalent); for under 2 years of age, concomitant low-dose steroid inhalants (300-400 µg if converted to BDP-CFC equivalent) in combination with $\beta_2$ stimulants (twice a day).


Featured in each Pharmacopoeia; may be searched (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, Japanese Pharmacopoeia).
13. Proposed (new/adapted) text for the WHO Model Formulary

At present, the following are featured in the WHO Model Formulary.

**Sodium cromoglicate**

Sodium cromoglicate is a representative anti-asthma drug.

Various drugs can serve as alternatives.

Sodium cromoglicate is a complementary drug.

*Aerosol inhalation* (pressured inhalation), sodium cromoglicate 5 mg/metered inhalation

**Uses:**

Prophylaxis of asthma; prevention of exercise-induced asthma

**Precautions:**

Pregnancy

(appropriate to use; see notes above and Appendix 2); Breastfeeding

(Appendix 3)

**Dosage:**

Prophylaxis of asthma and exercise-induced asthma, *by aerosol inhalation*

**ADULT** and **CHILD** 10 mg 4 times daily, increased in severe cases or during period of risk to 6-8 times daily; additional doses may be taken before exercise;

when stabilized, may be possible to reduce maintenance of 5 mg 4 times daily.

**Adverse effects:**

Coughing, transient bronchospasm