

Comments on Acetylsalicylic acid (ASA) from Expert Member

2. ANALGESICS, ANTIPYRETICS, NON-STEROIDAL ANTI-INFLAMMATORY MEDICINES (NSAIDs), MEDICINES USED TO TREAT GOUT AND DISEASE MODIFYING AGENTS IN RHEUMATOID DISORDERS (DMARDs)	
2.1 Non-opioids and non-steroidal anti-inflammatory medicines (NSAIDs)	
<i>Complementary List</i>	
<i>acetylsalicylic acid*</i>	<p><i>Suppository: 50 mg to 150 mg.</i></p> <p><i>Tablet: 100 mg to 500 mg.</i></p> <p><i>* For use for rheumatic fever, juvenile arthritis, Kawasaki disease.</i></p>

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2.1 Non-opioids and non-steroidal anti-inflammatory medicines (NSAIDs)	
acetylsalicylic acid	<p>Suppository: 50-150 mg.</p> <p>Tablet: 100-500 mg.</p>
ibuprofen	Tablet: 200 mg; 400 mg.

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Comment 1: Should a statement regarding the proper uses of ASA in children appear in the EML as well?

Discussion:

1. It is agreeable to list acetylsalicylic acid (ASA) in the complementary list and restrict its uses to only 3 indications i.e. rheumatic fever, juvenile arthritis and Kawasaki disease.
2. The decision above implies that ASA is not to be used in children at all for anti-pyretics and analgesics purposes (medium dose i.e. 30-50 mg/kg/day). Its uses are restricted for use in children only for anti-inflammatory (high dose i.e. 80-100 mg/kg/day) and anti-thrombotic effect (low dose i.e. 3-5 mg/kg/day) as in the long term treatment of Kawasaki disease.
3. In Thailand, since 2006 the Thai FDA banned all uses of ASA in children and adolescents (age 18 and lower) for fever, ache and pain. The uses of ASA in children are restricted for rheumatic fever, juvenile rheumatoid arthritis and Kawasaki disease.

ASA in powder form is cheap, widely distributed and very popular in Thailand. Cases of Reye's syndrome in children treated with ASA as self-medication in febrile illnesses given by caretakers are periodically reported.

4. Should a statement such as “*Not to be used for fever, ache and pain in children and adolescents to avoid Reye's syndrome. See proper uses of acetyl salicylic in EML for children.*” appear in the EML?

Comment 2: Should the lower dose range for ASA tablet be changed from 100 to 75 mg.?

1. The recommended dose for antiplatelet use of ASA starts from 75 mg. (BNF and US FDA)

BNF. A low dose of **aspirin** is used for the *secondary prevention* of thrombotic cerebrovascular or cardiovascular disease. A single dose of aspirin 150–300 mg is given as soon as possible after an ischaemic event, preferably dispersed in water or chewed. **The initial dose is followed by maintenance treatment with aspirin 75 mg daily.**

US FDA. •for acute coronary syndrome without ST-segment elevation (NSTEMI) including patients with unstable angina (UA):

Oral dosage:

Adults: **75-325 mg** PO non-enteric coated tablet, chewed and swallowed immediately, for patients without aspirin allergy. The maintenance dosage for secondary prevention is **75-162 mg** PO once daily indefinitely.

Comment 3: Should a statement regarding potential misuses of enteric coated ASA be added?

Discussion:

1. Enteric coated ASA may not be suitable for several indications due to its delayed absorption (2-5 hours) and delayed action.

Aspirin Safety and Overdose Information. Bayer HealthCare LLC.

Enteric coating is a delayed-release safety coating that provides added stomach protection. It is designed to allow the aspirin tablet or caplet to pass through the stomach to the small intestine (duodenum) before dissolving. This delayed release coating means that **it will take 2-5 hours for the**

aspirin to be absorbed. For this reason, **enteric coated aspirin is not recommended for quick pain relief.**

US FDA. •for acute coronary syndrome without ST-segment elevation (NSTEMI) including patients with unstable angina (UA):

Oral dosage:

Adults: 75-325 mg PO **non-enteric coated tablet, chewed and swallowed immediately**, for patients without aspirin allergy.

Comment 4. Enteric coated ASA has not been proved to be safer than plain tablets but it is more costly and probably ineffective in certain situations. Should any remark be made in the EML regarding the preferred dosage form of ASA?

Low dose aspirin - harm and benefits. Bandolier Knowledge. <http://www.jr2.ox.ac.uk/bandolier/band86/b86-2.html>

Enteric-coated aspirin had a similar risk associated with upper GI bleeding or perforation to plain aspirin (Table 1).

Table 1: Upper GI bleed with low-dose aspirin according to formulation

		Adjusted relative risk (95% CI)
All sites	Plain	1.9 (1.6 to 2.3)
	Coated	2.3 (1.6 to 3.2)
Gastric	Plain	2.0 (1.5 to 2.5)
	Coated	2.2 (1.4 to 3.6)
Duodenal	Plain	1.6 (1.3 to 2.1)
	Coated	2.2 (1.4 to 3.4)

Walker J, Robinson J, Stewart J, Jacob S. Does enteric-coated aspirin result in a lower incidence of gastrointestinal complications compared to normal aspirin? Interact Cardiovasc Thorac Surg. 2007 Aug;6(4):519-22. Epub 2007 Apr 6.

No clinical benefits in terms of reduction of gastrointestinal bleeding or ulceration **with enteric coating** have, therefore, been successfully demonstrated, although the endoscopic studies show that potentially these benefits could exist.

Of interest in the UK, the British National Formulary (www.bnf.org) lists the price of a 28-tablet pack of non-proprietary **aspirin to be 87p** and Caprin, a brand of **enteric-coated aspirin to be £1.55.**

1: [Stroke](#). 2006 Aug;37(8):2153-8. Epub 2006 Jun 22.

Effect of enteric coating on antiplatelet activity of low-dose aspirin in healthy volunteers.

Cox D, Maree AO, Dooley M, Conroy R, Byrne MF, Fitzgerald DJ.

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BACKGROUND AND PURPOSE: **Aspirin resistance may be relatively common** and associated with adverse outcome. Meta-analysis has clearly shown that 75 mg plain aspirin is the lowest effective dose; however, it is not known whether the recent increased use of enteric-coated aspirin could account for aspirin resistance.

CONCLUSIONS:

Equivalent doses of the enteric-coated aspirin were not as effective as plain aspirin. Lower bioavailability of these preparations and poor absorption from the higher pH environment of the small intestine may result in inadequate platelet inhibition, particularly in heavier subjects.

Maree AO, Curtin RJ, Dooley M, Conroy RM, Crean P, Cox D, Fitzgerald DJ. Platelet response to low-dose enteric-coated aspirin in patients with stable cardiovascular disease. J Am Coll Cardiol. 2005 Oct 4;46(7):1258-63. Department of Clinical Pharmacology, Royal College of Surgeons in Ireland, Dublin, Ireland.

Forty-four percent of patients had elevated serum TX B2 levels (>2.2 ng/ml). Arachidonic acid-induced platelet aggregation occurred more frequently in these patients (21% vs. 3%; $p = 0.004$). CONCLUSIONS: **Many patients** who are prescribed low-dose **enteric-coated (EC) aspirin** for secondary prevention of cardiovascular events have **persistent uninhibited platelet COX activity**. Younger and heavier patients and those with a previous MI are most likely to have an inadequate response to treatment.