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Acute sore throat revisited: clinical and experimental evidence for the efficacy of over-the-counter AMC/DCBA throat lozenges.

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3 **Acute sore throat revisited: clinical and experimental evidence for the efficacy of**
4 **over-the-counter AMC/DCBA throat lozenges.**
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Abstract (177 words)

Acute sore throat is a minor, self-limiting ailment, but patients commonly seek advice and treatment for immediate symptomatic relief. However, most sore throats due to upper respiratory tract infections are viral in nature, and antibiotics often prescribed are not suitable for the treatment of sore throat, as reflected in many European guidelines.

Many topical treatments are available over the counter, including throat sprays, gargles and lozenges. We discuss some of the 'ideal' features of over-the-counter options in the treatment of simple sore throat cases. The main features include the direct targeting of the viral and inflammatory causes, the provision of local pain relief, rapid onset of action and prolonged duration of action, effectiveness over a range of different types of sore throat, an ability to address the emotional aspects associated with having a sore throat and a good safety profile. Some recent clinical and experimental evidence on the efficacy and postulated mechanism of action for amylmetacresol and 2,4-dichlorobenzyl alcohol-containing lozenges, that have been marketed for many years are also discussed as an illustration of such targeted approach.

Introduction

Recent events of the human influenza (H1N1 virus) pandemic have exposed a central role for sore throat in the basic clinical presentation of the disease (1). 'Acute sore throat' is a term often used to describe pharyngitis, tonsillitis and laryngitis that occur for a short period of time. On average, regardless of a pandemic influenza year, an adult may experience 2–3 sore throats over a period of 12 months, whereas children are more susceptible and are likely to experience more sore throat episodes (2), because of their immune naivety. With the imminent re-emergence of flu season in the UK, it would appear an opportune moment to revisit the role of self-prescribed sore throat remedies that, alongside NHS Direct in the United Kingdom (UK), can alleviate pressures on general practitioners. The symptoms of sore throat vary between individuals and include a local mild discomfort with a scratchy-like sensation, swelling, pain with a 'raw' sensation and difficulty in swallowing (3). Most cases of acute sore throat due to upper respiratory tract infections (URTIs), caused by a range of viruses, are generally not serious and are self-limiting, usually improving within 1 week (3,4,5).

A recent report by the Royal College of General Practitioners in the UK documented an age-standardised person prevalence rate of 182 per 10,000 for acute pharyngitis in the year 2007. Furthermore, they reported a patient consultation rate of 182 per 10,000 persons for all ages (6). Current recommendations are to avoid unnecessary prescribing of antibiotics (7–10). Therefore, an understanding of the leading causes of sore throat and the availability of effective over-the-counter (OTC) treatment options as a recommendation for patients who present at surgeries, are becoming increasingly important.

Causes of acute sore throat

Viruses have been associated with 50–95% of sore throats in adults (11,12), and linked to 70% of sore throats in children between the ages of 5–16 years, and 95% in under 5s (12). The viral causes of sore throat are numerous and include respiratory viruses such as respiratory syncytial viruses, rhinoviruses and influenza A (13,14). A global analysis of the prevalence of patients with human influenza (H1N1 virus) reporting sore throat as a symptom ranged from 26% (in the UK) to 39% (in Japan) (1).

It is possible that bacterial causes may be underestimated and may contribute up to 20% of all sore throat aetiologies (15). Therefore, it is important that cases of sore throat due to streptococcal infections are correctly identified with appropriate antibiotics prescribed. Other

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3 causes of sore throat include environmental influences, such as temperature changes, low
4 humidity, smoking, air pollution and a reaction to allergens, among other factors (7).
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9 ***Pro-inflammatory cytokines and acute sore throat***

10 Irrespective of the cause, a sore throat manifests as irritating symptoms such as pain and
11 irritation, and is most likely to be caused by inflammatory mediators, e.g. bradykinin and
12 prostaglandins, which are released following local responses to cell damage and exert their
13 effect on sensory nerves in the airways (16). In addition, pro-inflammatory cytokines have
14 been associated with sickness behaviour (17), which, in turn, is associated with increased
15 pain sensitivity in cases of microbial infection (17). Because most sore throats are infective
16 in nature and sore throat-induced pro-inflammatory cytokines are linked with sickness
17 behaviour, there may be potential implications to the quality of life of sufferers where there is
18 associated viral or bacterial infection. A study in young adults with suspected viral sore
19 throat has demonstrated a high correlation between sore throat and 'sickness' (18).
20 Furthermore, it has been found that sore throats have a significant impact on normal daily
21 activities/functions of a patient, including swallowing, talking, eating a meal, sleeping and
22 concentration (19).
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34 **Associated cost burden**

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37 Despite the high predominance of viral sore throats over any other causes in adults (11,12),
38 antibiotics are commonly prescribed by physicians for the treatment of acute sore throats
39 (20,21). Throughout the 1980s, there was a progressive increase in the overall consumption
40 of antibiotics in the UK (20,22). Although this number fell by 45% in the mid-1990s, in the
41 year 2000, antibiotics were still prescribed to over two-thirds of patients presenting to
42 general practice with respiratory tract infections; 60% of whom had sore throat (20).
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49 It is now generally recognised that antibiotics have limited efficacy in the majority of patients
50 with acute sore throats (7,21), and may encourage repeated attendance for future sore
51 throat episodes (23). The World Health Organisation guidelines have discouraged the
52 prescribing of antibiotics for the treatment of viral sore throat (7). The National Institute for
53 Health and Clinical Excellence (NICE) guidelines in the UK have recommended no or
54 delayed prescribing of antibiotics for minor acute illnesses, including sore throat (8).
55 Furthermore, reduced antibiotic prescribing may curb the development of antibiotic-
56 resistance in the community (11) and reduce the overall cost burden on the healthcare
57 system. Delaying the prescribing of antibiotics (i.e. using antibiotics only if symptoms
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3 worsen) in cases of acute sore throat was deemed cost-effective, thereby offering cost
4 savings to the healthcare system (8). For example, by adopting the recommended
5 prescribing strategies of delayed or no prescribing, more than £30 can be saved per patient
6 compared with the cost of immediate antibiotic prescribing (8).
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10 11 12 **Self-management of acute sore throat**

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15 Most cases of acute sore throat can be managed effectively by the patient who does not
16 present with signs of complications such as fever and difficulty in breathing (with the
17 exception of children). The management of acute sore throat revolves around providing relief
18 from existing symptoms (e.g. local pain and inflammation), removal of the underlying causes
19 and the prevention of secondary complications (3). Self-management of non-complicated,
20 simple cases of acute sore throat is possible through the use of analgesic, local anaesthetic,
21 antiseptic and anti-inflammatory agents.
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29 ***Available OTC sore throat remedies and the different formulations***

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31 Compared with oral analgesic treatments, topical remedies such as throat lozenges, gargles
32 and throat sprays (3), which are applied directly to the mucous membranes of the mouth or
33 throat, can provide more rapid symptomatic relief in patients with acute sore throat. There
34 are clear differences between the three topical delivery systems in the onset of action and
35 the amount of active ingredients present in the mouth and throat. Throat sprays should
36 ideally produce relatively coarse droplets so that they reach the desired target site. However,
37 a proportion of the spray is immediately swallowed after application (24), thus reducing the
38 concentration of active ingredients present in the mouth and throat. In addition, evidence
39 suggests that owing to the gag reflex, gargles are not able to deliver the active ingredients to
40 all areas of the throat and only deliver to the anterior oral cavity (25).
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49 Lozenges are placed in the oral cavity where they slowly dissolve to release the active
50 ingredients directly onto the irritated mucosal tissues. As the lozenge dissolves in the mouth,
51 the mouth adopts a reservoir-like role for the distribution of the lozenge contents to the throat
52 (24). Therefore, medicated throat lozenges have the added advantage of being slow-
53 releasing. Furthermore, the portability and convenience of taking lozenges may help to
54 facilitate good adherence/compliance to medication.
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60 A range of active ingredients are used in topical OTC sore throat remedies (Table 1). It is not
our intention to present clinical evidence for each of the sore throat treatments available

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OTC. However, we will use amylmetacresol and 2,4-dichlorobenzyl alcohol (AMC/DCBA)-containing throat lozenges as a case example because of the availability of recently published data/evidence.

Important features of some topical OTC sore throat remedies

We propose that an ideal sore throat treatment, or a range of treatment products, should possess the following properties:

- Targets the causes of throat soreness, especially the viral causes and inflammation
- Provides local pain relief, eliminating the associated discomfort in the throat region
- Provides a rapid onset of action from the time that the remedy is taken or administered
- Has a prolonged duration of action, given the actual and patient-perceived prolonged nature of sore throat symptoms
- Be shown to be effective over a range of different types of sore throat (e.g. from the scratchy-like sensation causing local discomfort to the painful sore throats with a 'raw' feeling and to the inflamed, swollen throat types of sore throat)
- Should address the emotional aspects of having a sore throat by helping patients to feel better
- Should have a good safety profile

We will now consider these seven characteristics in greater detail.

Targeting the causes of sore throat

Several antiviral drugs of the neuraminidase inhibitor class have been shown to block the replication of influenza in the upper airways (14,50), and thereby reduce the symptoms, including those of sore throat. However, although antiviral treatments may have a pivotal place in the treatment of URTIs (51), they are bound by several limitations. For example, they are limited by the specific nature of antiviral drugs, the fact that new strains are constantly emerging, the length of time an anti-infective takes to work and the subsequent level of reduction in inflammation that is required before clinical benefits prevail. Moreover, from the viewpoint of a patient, being able to feel well quickly is of primary importance, and so the availability of treatment (i.e. OTC, for easy access and self-management) that targets the underlying causes of sore throat to provide rapid symptomatic relief is key. Ideally, such treatments would target both the viral and inflammatory causes because evidence suggests that antiviral without anti-inflammatory effects have little symptomatic benefit for patients with a cold (52).

Pain relief

Local symptomatic pain relief plays an important role in the management of acute sore throat (51). The influence of pro-inflammatory mediators on the pain sensation of all sore throats regardless of the cause need to be taken into consideration when making treatment choices, and should also be a target for providing symptomatic relief of symptoms, thereby reducing associated inflammation and pain.

The analgesic effect experienced with antiseptic lozenges such as AMC/DCBA throat lozenges was thought to be produced by means of its antiseptic action on bacteria and viruses (Figure 1) (13,53,54). *In vitro* evidence demonstrated the virucidal effect of AMC and DCBA on a number of viruses associated with common cold/flu (13), and it could be anticipated that reduction of virus infectivity in saliva would reduce virus transmission to others in addition to the immediate clinical benefits of reducing soreness. However, clinical trials and human quarantine experiments would be needed to precisely quantify the antiviral effects of any lozenge *in vivo*.

However, recent evidence has led to the theory that such pain relief was not merely as a result of antiseptic and demulcent/moisturising action – a possible sodium channel-blocking effect was deemed to be a contributory factor and a viable mechanistic pathway (29). Sodium channels, as mediators of membrane excitability, regulate the sodium permeability of cells during the rapid rising phase of the action potential. These channels play a key role in initiation and transmission of electrical activity throughout the nervous system, with implications for sensory neuron physiology and pathophysiology, and localised inhibition of their function can prevent the perception of pain (55,56). Therefore, sodium channels are thought to represent key target sites for local anaesthetic agents, such as lidocaine, to exert their analgesic effects.

Based on previous work on sodium channel-blocking properties of phenol derivatives (57–59), we hypothesised that the analgesic effect of antiseptics which carry the aromatic alcohol phenol as the core element (see Figure 2) might actually – at least partly – be due to sodium channel blocking, i.e. direct local anaesthetic-like effects.

In particular, the proposition was examined that the active ingredients AMC, DCBA and hexylresorcinol present in some antiseptic lozenges act in this manner. When the *in vitro* effect of AMC, DCBA and hexylresorcinol in blocking voltage-operated neuronal sodium channels heterogeneously expressed in human embryonic kidney 293 cells was investigated (29), all three agents were found to block voltage-gated sodium channels in a local

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3 anaesthetic-like fashion. When AMC and DCBA were investigated separately and in
4 combination, AMC inhibited sodium inward current with a high potency; DCBA, although
5 lower in potency than AMC, exhibited similar blocking potency to the local anaesthetic,
6 lidocaine (29). A combination of the potent channel blocker, AMC, and the reduced potency
7 for sodium channel blockade of DCBA attenuated the effects of AMC, possibly as a result of
8 competitive binding. This may have *in vivo* benefits of limiting the overall local anaesthetic
9 effect known as a 'ceiling' effect, so as to avoid over-numbing without compromising pain
10 relief (29).
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18 In addition, real-life patient experiences reported during clinical trials have demonstrated that
19 AMC/DCBA-containing lozenges exert significantly greater reductions in mean throat
20 discomfort levels (60), severity of throat soreness (19,60–62), offering greater pain relief
21 (19,60–62) and easing of difficulty in swallowing (19) to sore throat sufferers compared with
22 non-medicated placebo lozenges. Furthermore, the analgesic effects of AMC/DCBA throat
23 lozenges were clinically meaningful compared with non-medicated lozenges (19), and
24 significant improvements in functional impairment scores were observed for swallowing,
25 talking and eating a meal (19). Importantly, this evidence suggests that effective OTC
26 treatments are available that not only provide effective relief of the physical symptoms, but
27 also improve functional impairment, thus allowing patients to re-engage in their daily
28 activities and return to their everyday lives (19).
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39 **Speed of action**

40 When evaluating the suitability of sore throat remedies, the simple demulcent benefits
41 should not be overlooked because demulcents, such as glycerin, honey and sugar (which
42 form the base of throat lozenges), act to soothe the throat and reduce the irritation (2). In
43 addition, the increased production of saliva induced by the sucking action required with
44 lozenges that becomes evident after 1 minute (63) provides lubrication to the throat to
45 soothe inflammation (2). Saliva production may also flush the offending microbes from the
46 throat surface (2). Furthermore, the antiviral and antifungal constituents of saliva may protect
47 tissues by targeting microbes, encouraging soft tissue repair, maintaining an ecological
48 balance in the oral region and maintaining an adequate pH (64). Previous research has
49 shown that AMC/DCBA-containing throat lozenges administered to healthy volunteers
50 promote saliva production (63).
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Scintigraphy studies have highlighted transit and deposition sites in the throat and have
shown that the lozenge formulation can facilitate the delivery of active ingredients to the

throat at a similar rate to a spray and at a greater rate than a gargle, and at a concentration that was maintained for longer than the spray or gargle (24).

In general, rapid sensorial effects (i.e. relief that is soothing and comforting) can impact the overall speed of treatment benefit, and is thus key to the perceived efficacy of a sore throat remedy. However, the sensorial effects will also need to be supported by rapid analgesic relief provided by the active ingredients – this separation of effect can be seen with AMC/DCBA throat lozenges (19). Furthermore, because the natural clinical course of sore throats is often 6–8 days (18), untreated patients often endure persistent pain, irritation or other unpleasant sensory experiences over a prolonged period of time.

The duration of action

Therefore, having a long duration of action is an essential prerequisite of any remedy used.

Limb *et al.* have demonstrated that lozenges offer a relatively prolonged activity (23). Gargles are usually gargled in the mouth for approximately 30 seconds and then are expelled whereas sprays are swallowed soon after application, but lozenges take approximately 6–9 minutes to dissolve in the mouth upon sucking (63). Scintigraphy research has shown that lozenges are an ideal vehicle for sore throat treatment owing to their reservoir-like action, offering rapid and prolonged delivery of active ingredients (24). Furthermore, studies have demonstrated that continued use of AMC/DCBA throat lozenges over a 3-day period provides significantly greater improvements in throat soreness, faster pain relief and greater easing of difficulty in swallowing compared with non-medicated lozenges (19).

Effectiveness over a range of different types of sore throat

Sore throats exhibit themselves in different ways depending on the individual and the causative factors. A combination of antiseptic, analgesic and anti-inflammatory properties of medicated lozenges, and stimulation saliva production are important attributes for a sore throat lozenge.

Helping patients to feel better

McNally *et al.* have recently documented the beneficial effects of a lozenge and noted that a significantly greater number of patients who took the medicated throat lozenges felt better compared with those who took the non-medicated lozenge (65% vs 26%, respectively;

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3 P<0.0001) (19). This begins to address the emotional aspects of having a sore throat. When
4 patients feel better, they can get back to and carry on with their everyday lives.
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8 9 **Safety profile**

10 The literature available on topical OTC sore throat treatments demonstrates a good safety
11 profile, with only very minor self-limiting adverse effects, such as headaches and coughing
12 being reported. However, a systematic review is warranted to further evaluate this.
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14 Additionally, it is important to note that patients should take care when drinking hot
15 beverages if using strong anaesthetics, because the local numbing effect may result in
16 patients underestimating the exact temperatures.
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22 23 **Conclusions**

24 Sore throat is considered a minor ailment but results in considerable suffering for the patient
25 who then seeks remedial action, often at the expense of the healthcare system. A reduction
26 in antibiotic prescribing, especially for respiratory conditions such as sore throat, is currently
27 on the agenda of many global healthcare services to minimise bacterial resistance and
28 unnecessary exposure of patients to potential side effects (7–9, 20), which in turn reduces
29 costs. In the UK, NHS Direct has encouraged self-diagnosis and along with the mild
30 symptoms (including sore throat) experienced by most, the extensive OTC range of
31 medicines, such as analgesics and sore throat lozenges has played an important clinical role
32 in communities around the world.
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40 An 'ideal' OTC treatment for sore throat should have a minimum set of features that would
41 render it clinically effective in providing pain relief and have additional benefits, such as
42 those of sensorial stimulation. These 'ideal' characteristics – targeting the underlying causes,
43 providing pain relief, having a rapid onset of action or prolonged duration and being effective
44 over a range of different sore throat types such that the patient feels better after treatment –
45 should be borne in mind when making a treatment recommendation to patients, given the
46 evidence available.
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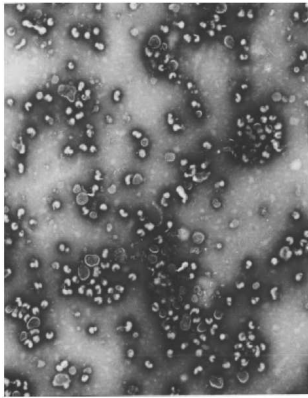
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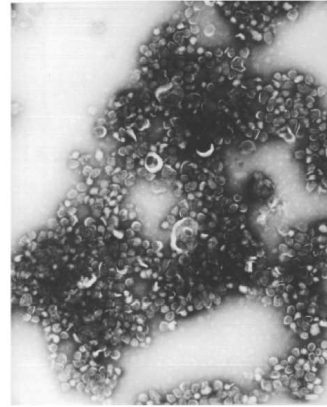
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Figure 1: The mechanism of action of AMC/DCBA-induced destruction of viruses (13)

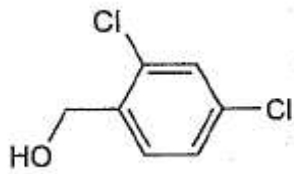
A. Control virions incubated for 4 minutes in artificial saliva buffer solution. Virions are evenly distributed. (Magnification approximately 9k)



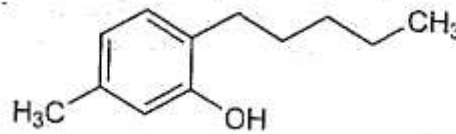
B. Control virions incubated for 4 minutes with the virucidal lozenge mixture. Note clumped virions. (Magnification approximately 9k)



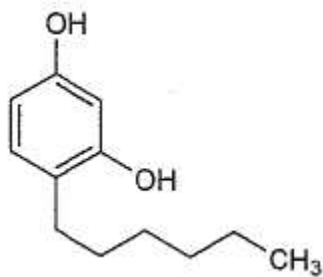
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3 **Figure 2: Structures of AMC, DCBA and hexylresorcinol**
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14 2,4-dichloro-benzylalcohol



24 Amylmetacresol



Hexylresorcinol

Table 1: Main active ingredients present in some typical OTC sore throat treatments and their mode of action

Active ingredient	Formulation type(s)	Products containing these ingredients*	Mechanism of action	References
Ambroxol hydrochloride	Lozenges	Mucoangin™	Local anaesthetic; acts on the neuronal voltage-gated Na channels in sensory neurones (29)	Weiser and Wilson, 2002 (26); Schutz <i>et al</i> , 2002 (27); Fischer <i>et al</i> , 2002 (28)
Amylmetacresol	Spray, lozenges	Strepsils®	Antibacterial; antiviral; local anaesthetic; blocks voltage-gated Na channels in a local anaesthetic-like manner	Buchholz <i>et al</i> , 2009 (29)
Benzocaine (ethylaminobenzoate)	Cream, gel, spray, lozenges	Merocaine®; Tyrozet®; Chloraseptic; Dequacaine®	Local anaesthetic (ester-type)	Dempster, 1988 (30); Kagan <i>et al</i> , 1982 (31)
Benzydamine HCl	Throat spray, gargles, lozenges	Tantum Verde, Difflam	Non-steroidal anti-inflammatory drug (NSAID); some local anaesthetic activity	Froom and Boisseau, 1979 (32); Wethington, 1985 (33); Young, 1987 (34); Chudoba, 1983 (35); Whiteside, 1982 (36); Agarwal <i>et al</i> , 2006 (37)
Cetylpyridinium chloride	Lozenges, throat sprays	Merocets®, Merocaine®	Antibacterial	Richards <i>et al</i> , 1996 (38); Zejdl <i>et al</i> , 1990 (39)
2,4-dichlorobenzyl alcohol	Spray, lozenges	Strepsils®	Antibacterial; antiviral; local anaesthetic; blocks voltage-gated Na channels in a local anaesthetic-like manner	Buchholz <i>et al</i> , 2009 (29)
Flurbiprofen	Sprays, gargle, lozenges	Strefen®	Anti-inflammatory; NSAID	Benrimoj <i>et al</i> , 2001 (40); Watson <i>et al</i> , 2000 (41); Blagden, 2002 (42)
Hexetidine	Throat spray, mouth spray, lozenges	Hexoral	Antiseptic effects	Bokor, 1996 (43); Klingbeil, 1982 (44)
Hexylresorcinol	Lozenges	Strepsils Extra®	Antiseptic; local anaesthetic; blocks voltage-gated Na channels in a local anaesthetic-like manner	Martindale 35 th Ed, 2007 (45); Buchholz <i>et al</i> , 2009 (29)
Lidocaine HCl	Spray, gel, lozenges	Strepsils Plus®, Dequaspray	Local anaesthetic (amide-type): blocks voltage-gated Na channels	Martindale 35 th Ed, 2007 (45); Leuwer <i>et al</i> , 2004 (46); Buchholz <i>et al</i> , 2009 (29)
Muramidase HCl (lysozyme)	Lozenges, mouth rinses	Lysopaine	Antibacterial; hydrolysis of glycosidic linkage of peptoglycan in bacterial cell walls	Bienen and Raus, 1981 (47)
Volatile oils (i.e. menthol)	Lozenges	Halls, Locketts	Antibacterial, local anaesthetic; blocks voltage-gated Na channels	Al-Bayati, 2009 (48); Martindale 35 th Ed, 2007 (45); Haeseler <i>et al</i> , 2002 (49)

*Not all products are licensed for OTC sale in every country