

Locally Delivered Flurbiprofen 8.75 mg for Treatment and Prevention of Sore Throat: A Narrative Review of Clinical Studies

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Background: Antibiotics are inappropriately prescribed to many people with sore throat. As most cases of sore throat are viral and/or self-limiting, guidelines recommend symptomatic management as first-line treatment. This paper reviews the available clinical evidence for the efficacy and safety of low-dose (8.75 mg) flurbiprofen, locally delivered to the throat for the symptomatic management of pharyngitis/sore throat.

Method: A literature search was performed on 27 February 2019 using PubMed. Studies that met the following criteria were included in a narrative review: (1) studies evaluating the effectiveness of flurbiprofen for pharyngitis/sore throat; (2) randomized controlled studies; (3) locally administered formulation of study drug/comparator; and (4) flurbiprofen administered at 8.75 mg dose (single- or multiple-dose administration).

Results: A total of 17 papers were included in the review: 15 publications reporting data from nine unique clinical studies of flurbiprofen for acute pharyngitis, and two reporting studies of flurbiprofen for the prevention of postoperative sore throat (POST). Studies in acute pharyngitis demonstrated that single- and multiple-dose flurbiprofen 8.75 mg, locally administered in lozenge, spray or microgranule form, was well tolerated and provided early onset and long-lasting symptomatic relief from throat pain and soreness, sensation of swollen throat, difficulty swallowing, and other associated symptoms. This included patients with more severe symptoms, patients with confirmed *Streptococcus* A/C sore throat, and patients taking concomitant antibiotics. In addition, a single preoperative dose of flurbiprofen lozenge was shown to be effective for relieving early POST in patients undergoing general anesthesia.

Conclusion: Locally administered, low-dose flurbiprofen offers a useful first-line treatment option for symptomatic relief in patients with “uncomplicated” acute pharyngitis/sore throat associated with upper respiratory tract infection, thus potentially helping to reduce unnecessary antibiotic prescribing. It also offers an effective preoperative treatment option for the reduction of early POST severity and incidence.

Keywords: flurbiprofen, pharyngitis, sore throat, lozenge, spray, pain relief

Introduction

Pharyngitis is one of the most common reasons patients seek advice from a healthcare provider (HCP) in primary care.¹ Although not life-threatening, pharyngitis, particularly symptoms such as sore throat, can have a substantial negative impact on an individual's daily life.² Relief from the severe symptoms of pharyngitis are a key driver of patients' consultations with HCPs, and of antibiotic-seeking behavior,^{3,4} with complaints of sore throat constituting between 1% and 4% of all primary care

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presentations internationally.^{5,6} Pharyngitis is generally of infectious etiology, with the vast majority of cases caused by self-limiting viral infections.⁷ Only around 5–30% of cases are attributed to bacterial etiologies – with approximately 10% to group A β -hemolytic *Streptococcus pyogenes* (strep A)^{7–10} – although other bacteria, including *Streptococcus dysgalactiae* (strep C), have been implicated.⁹ Pharyngitis symptoms typically last 3–7 days,¹¹ but are often worst during the first few days.^{12,13} The natural course of pharyngitis is similar in most patients, regardless of whether they are strep positive or not.¹⁴

Guidelines recommend symptomatic management of pharyngitis as a first-line treatment, and suggest avoiding or delaying antibiotic use in acute pharyngitis, except in the minority of patients with more severe strep infection or risk factors for serious complications such as rheumatic fever.^{15,16} The availability of rapid and effective symptomatic relief is, therefore, an important factor in meeting patients' expectations and avoiding unnecessary use of antibiotics;³ most cases of pharyngitis can be managed by patients using over-the-counter (OTC) treatments as a means of controlling their symptoms.^{15,16} As inflammation is the underlying cause of pharyngitis,¹² treatment of the condition with a nonsteroidal anti-inflammatory drug (NSAID) can offer rapid and long-lasting relief from pain.^{17,18}

To minimize the potential risk of an adverse event, regulatory bodies and medical societies recommend using the lowest effective NSAID dose for the shortest time necessary to control symptoms.¹⁹ Locally administered formulations of NSAIDs, such as lozenges and sprays, facilitate targeted application of active ingredient to the throat,²⁰ allowing absorption of the drug directly where it is needed.²¹ This allows administration of a lower dose than systemic therapy,²² reducing the potential for adverse effects.^{23,24} Flurbiprofen is an NSAID that has been formulated for local delivery at a low dose and is commercially available as a single active ingredient in both lozenge and spray formulations.^{25,26} It is most commonly used at a dose of 8.75 mg, based on the results of a dose-ranging study that demonstrated linear dose–response relationships for effectiveness and adverse events at doses between 5.0 mg and 12.5 mg.²⁷ Its use for the symptomatic relief of pharyngitis of viral, bacterial, or unknown etiology has been assessed in a number of studies.^{17,22,25,26,28–38} It has also been evaluated for the relief of postoperative sore throat POST,^{39–41} a common complication of general anesthesia⁴² and tonsillectomy⁴³ that can negatively impact patients' postoperative comfort.

The aim of this paper is to review the available clinical evidence for the efficacy and safety of low-dose (8.75 mg) flurbiprofen, locally delivered to the throat for the symptomatic management of pharyngitis/sore throat. This review predominantly focuses on the management of sore throat associated with upper respiratory tract infection (URTI); its use for POST prevention is discussed in brief.

Methods

Search Strategy

A literature search was performed on 27 February 2019 using PubMed (including MEDLINE), with a search string including the following: “flurbiprofen” [MeSH term] AND (“pharyngitis” [MeSH term] OR (“sore” [all fields] AND “throat” [all fields]) OR “sore throat” [all fields] OR “postoperative” [all fields]). No date limits were applied. The titles and abstracts of the retrieved references were screened against the following predefined inclusion criteria:

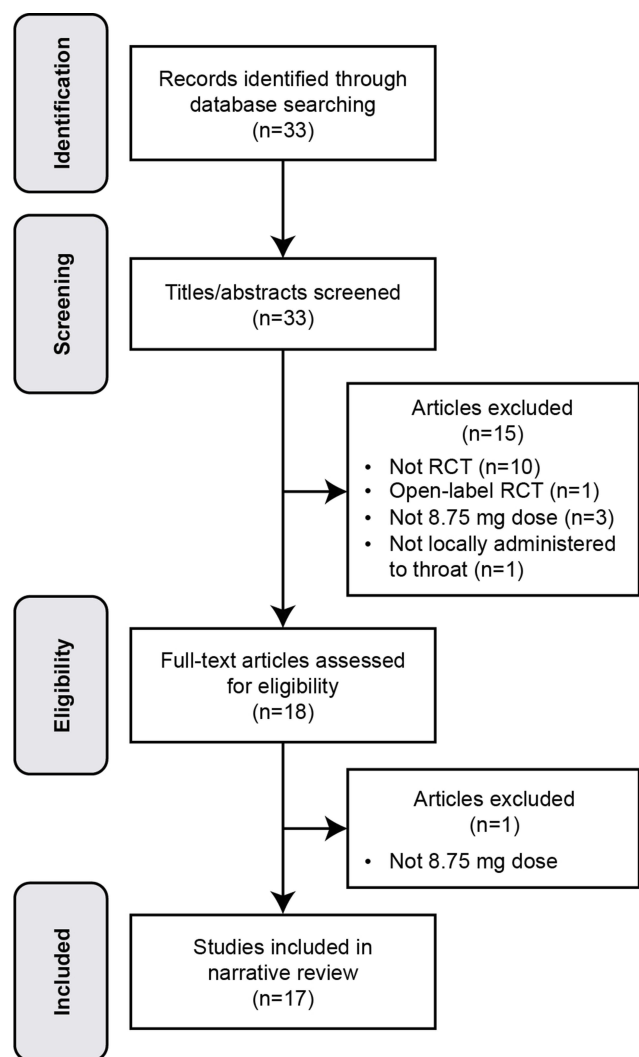
- Studies evaluating the effectiveness of flurbiprofen for pharyngitis/sore throat
- Randomized controlled studies
- Locally administered formulation of study drug/comparator
- Flurbiprofen administered at 8.75 mg dose (single- or multiple-dose administration)

The full text of all potentially relevant publications was then reviewed to confirm inclusion and to determine whether a meta-analysis of the data was feasible. If a meta-analysis was not deemed possible, a narrative review of the evidence would be performed.

Results

The PubMed search identified 33 unique records, of which 15 were excluded as they did not meet the inclusion criteria based on title/abstract screening (Figure 1). A total of 18 records underwent full text assessment: 17 were selected for inclusion in the final review (Table 1), and one study in POST was excluded as it evaluated a flurbiprofen dose lower than 8.75 mg.³⁹

In view of the heterogeneity of the data reported in the studies identified, it was not possible to conduct a meta-analysis. For example, studies varied with regard to the formulation by which the active ingredient was administered (lozenge, spray, and microgranules), the outcome measures investigated, the nature of data reported (some



RCT, randomized controlled trial

Figure 1 Publication assessment process.

studies reported baseline and endpoint data, whereas others only reported efficacy in terms of percentage change from baseline) and the data reporting units. A narrative review was therefore determined to be the appropriate methodology.

Acute Pharyngitis

Fifteen publications, reporting data from nine unique clinical studies of flurbiprofen for acute pharyngitis, were included in this review (Table 1). Ten publications reported data for flurbiprofen lozenges vs placebo, two reported data for flurbiprofen spray vs placebo, two compared flurbiprofen lozenges and spray, and one reported data for flurbiprofen microgranules vs placebo. All flurbiprofen study medications were provided by Reckitt Benckiser. All studies included

adult patients with confirmed pharyngitis due to URTI, with the exception of one study including patients aged 12 years and over which did not specifically screen for URTI.³¹ Patients were eligible for inclusion if they reported acute onset of pharyngitis (range: 3–7 days or less) and moderate to severe symptoms. The effectiveness of flurbiprofen has been assessed using several different outcome measures; Table 2 provides descriptions of the key endpoint measures and tools used in the included studies.

Throat Pain and Soreness

Overall, flurbiprofen 8.75 mg generally provided significant relief of sore throat pain and soreness compared with placebo (Table 3), as measured on the Sore Throat Pain Intensity Scale (STPIS), Sore Throat Relief Rating Scale (STRRS), Throat Soreness Scale (TSS) and Sore Throat Scale (STS) (Table 2).

Single Dose

Fourteen papers reported data on the effectiveness of single-dose flurbiprofen 8.75 mg for relieving throat pain and soreness;^{17,22,25,26,28–35,37,38} 11 included data for flurbiprofen lozenges, four for flurbiprofen spray and one for flurbiprofen microgranules. In a study by Schachtel et al,¹⁷ single-dose flurbiprofen lozenge demonstrated a significantly greater reduction (85%) in sore throat pain intensity summed over the 2 h post-dose period (as measured on the STPIS) compared with placebo ($p<0.001$). Moreover, in another study by Schachtel et al,³⁵ almost all (97%) patients treated with a single flurbiprofen lozenge experienced a reduction in sore throat pain intensity over the 3 h post-dose period (vs 76% of placebo-treated patients; $p<0.01$). Several other papers also reported significantly greater reductions in sore throat pain intensity compared with placebo with single-dose flurbiprofen lozenge,^{29,30,37} spray,³⁴ and microgranules³⁸ for up to 3–6 h post-dose (specific percentage reductions were not provided). Regarding absolute/percentage reductions in sore throat pain intensity/soreness from baseline, significantly greater reductions were observed with flurbiprofen vs placebo at all individual time-points up to 2–4 h in several studies.^{17,22,29–35,37} Radkova et al²⁶ observed an STPIS pain intensity difference from baseline to 2 h post-dose of -40.51 and -40.10 with flurbiprofen spray and lozenges, respectively. No significant difference was observed between single-dose flurbiprofen spray and lozenge in terms of improvement in sore throat pain intensity.^{25,26}

Table 1 Summary of Studies Included in the Narrative Review

Reference	Formulation	Population	Dosing (Assessment Period)	Subgroups of Interest	Key Reported Outcome Measures
Acute pharyngitis studies					
Randomized, double-blind, single-dose, placebo-controlled, single-center study to assess the efficacy of flurbiprofen 8.75 mg lozenges in patients with acute sore throat (NCT01986361)					
Schachtel, Pain Manag 2018 ²⁸	Lozenge	Flurbiprofen (n=101) Placebo (n=21)	Single dose (3 h)	Strep/non-strep	• STS • QuaSTI • URTI questionnaire
Schachtel, Br J Pain 2018 ³⁵	Lozenge	Flurbiprofen (n=101) Placebo (n=21)	Single dose (3 h)	Strep/non-strep Severe sore throat	• Time to meaningful pain relief • Time of first perceived pain relief (measured on STS and STPIS)
Randomized, double-blind, placebo-controlled, multiple-dose, single-center, parallel-group study of the efficacy of flurbiprofen 8.75 mg lozenges compared with placebo lozenges in adult patients with acute sore throat (NCT01049334)					
Schachtel, Pain 2014 ¹⁷	Lozenge	Flurbiprofen (n=102) Placebo (n=102)	Single dose (6 h)		• STPIS (SPID over 2 h) • DSS • SwoTS • STRRS
Aspley, Curr Med Res Opin 2016 ²⁹	Lozenge	Flurbiprofen (n=59) Placebo (n=65)	Single dose (6 h) Multiple dose: 1 every 3–6 h as needed (up to 5 in 24 h) for up to 7 days (24 h)	Severe sore throat	• STPIS (SPID over 24 h) • DSS • SwoTS
Schachtel, Pain Manag 2016 ³⁶	Lozenge	Flurbiprofen (n=102) Placebo (n=102)	Multiple dose: 1 every 3–6 h as needed (up to 5 in 24 h) for up to 7 days (24 h and 7 days)		• STPIS (SPID over 24 h) • DSS • SwoTS • GLOBAL/SATIS
Shephard, Int J Clin Pract 2015 ^{37a}	Lozenge	Flurbiprofen (n=203) Placebo (n=199)	Single dose (6 h) Multiple dose: 1 every 3–6 h as needed (up to 5 in 24 h) for up to 7 days (24 h)	Strep/non-strep	• STPIS • DSS • SwoTS
Randomized, double-blind, placebo-controlled, parallel-group study to examine the efficacy and safety of multiple doses of flurbiprofen 8.75 mg lozenge, with a focus on the initial 24 h of treatment (NCT01048866)					
Schachtel, Trials 2014 ³⁰	Lozenge	Flurbiprofen (n=101) Placebo (n=97)	Single dose (6 h) Multiple dose: 1 every 3–6 h as needed (up to 5 in 24 h) for up to 7 days (24 h and 7 days)		• STPIS (SPID over 24 h) • DSS • SwoTS • STRRS • SATIS
Shephard, Int J Clin Pract 2015 ^{37a}	See above. Combined data from NCT01048866 and NCT01049334.				
Randomized, double-blind, parallel-group, placebo-controlled, multiple-dose, multicenter study to assess the efficacy and safety of flurbiprofen 8.75 mg lozenges in patients with sore throat in UK general practice					
Blagden, Int J Clin Pract 2002 ³¹	Lozenge	Flurbiprofen (n=230) Placebo (n=229)	Single dose (2 h) Multiple dose: 1 every 3–6 h as needed (up to 5 in 24 h) for up to 5 days (4 days)	Concomitant antibiotic use	• STRRS (TOTPAR) • TSS • DSS • SwoTS • Overall lozenge rating

(Continued)

Table 1 (Continued).

Reference	Formulation	Population	Dosing (Assessment Period)	Subgroups of Interest	Key Reported Outcome Measures
Randomized, double-blind, parallel-group, single-center study comparing the efficacy and tolerability of flurbiprofen lozenges (8.75 mg or 12.5 mg) with placebo in the treatment of patients with sore throat due to upper respiratory tract infection					
Benrimoj, Clin Drug Investig 2001 ³²	Lozenge	Flurbiprofen 8.75 mg (n=128) Flurbiprofen 12.5 mg (n=64) Placebo (n=128)	Single dose (6 h) Multiple dose: 6 h after first dose, 1 every 3 h as needed (up to 8 in 24 h) for up to 5 days (tolerability only, 5 days)		• STRRS (TOTPAR) • TSS • SwOTS • Overall treatment rating
Randomized, double-blind, parallel-group, placebo-controlled, single- and multiple-dose, single-center study to assess the efficacy and safety of flurbiprofen 8.75 mg and 12.5 mg lozenges in patients with relatively severe sore throat due to upper respiratory tract infection					
Watson, Int J Clin Pract 2000 ²²	Lozenge	Flurbiprofen 8.75 mg (n=129) Flurbiprofen 12.5 mg (n=43) Placebo (n=129)	Single dose (6 h) Multiple-dose: 6 h after first dose, 1 every 3 h as needed (up to 8 in 24 h) for up to 5 days (4 days)		• STRRS (TOTPAR) • TSS • SwOTS • Overall treatment rating
Randomized, double-blind, placebo-controlled, parallel-group study to assess the efficacy of flurbiprofen 8.75 mg spray in adults with sore throat due to upper respiratory tract infection (ACTRN12612000457842)					
de Looze, Eur J Gen Pract 2016 ³⁴	Spray	Flurbiprofen (n=249) Placebo (n=256)	Single dose (6 h) Multiple dose: 6 h after first dose, 1 every 3–6 h as needed (up to 5 in 24 h) for up to 3 days (3 days)		• TSS • TPS • DSS • SwOTS • STPIS (SPID) • STRRS (TOTPAR) • GLOBAL • SATIS
de Looze, Pain Manag 2018 ³³	Spray	Flurbiprofen (n=249) Placebo (n=256)	Single dose (6 h) Multiple-dose: 6 h after first dose, 1 every 3–6 h as needed (up to 5 in 24 h) for up to 3 days (not assessed)		• STRRS (TOTPAR) • Time to reporting 'at least moderate' relief lasting ≥30 min • SATIS
Multicenter, double-blind, double-dummy, non-inferiority study to assess the efficacy of flurbiprofen 8.75 mg delivered as a spray or lozenge in patients with sore throat due to upper respiratory tract infection					
Radkova, J Pain Res 2017 ²⁶	Spray and lozenge	Flurbiprofen spray (n=218) Flurbiprofen lozenge (n=222)	Single dose (2 h)	Strep/non-strep	• STPIS (SPID over 2 h) • SATIS • CLIN
Burova, J Pain Res 2018 ²⁵	Spray and lozenge	Flurbiprofen spray (n=218) Flurbiprofen lozenge (n=222)	Single dose (2 h)		• STRRS (TOTPAR) • DSS • SwOTS • URTI questionnaire • QuaSTI • GLOBAL
Randomized, double-blind, placebo-controlled, multiple-dose, multicenter study to determine the analgesic efficacy of flurbiprofen 8.75 mg microgranules vs placebo for patients with sore throat due to upper respiratory tract infection					
Russo, Br J Gen Pract 2013 ³⁸	Microgranules	Flurbiprofen (n=186) Placebo (n=187)	Single dose (6 h) Multiple dose: 6 h after first dose, 1 every 3–6 h as needed (up to 5 in 24 h) for up to 3 days (3 days)		• TSS • DSS • STPIS • STRRS • Consumer questionnaire

(Continued)

Table 1 (Continued).

Reference	Formulation	Population	Dosing (Assessment Period)	Subgroups of Interest	Key Reported Outcome Measures
Post-operative sore throat studies					
Double-blind, randomized, placebo-controlled study to evaluate the effect of flurbiprofen 8.75 mg lozenges on POST, hoarseness, and dysphagia symptoms of patients in whom a ProSeal LMA was inserted during general anesthesia					
Uztüre, Turk J Anaesth Reanim 2014 ⁴¹	Lozenge	Flurbiprofen (n=40) Placebo (n=40)	Single dose, 45 min before induction of anesthesia (24 h)	Surgical patients undergoing general anesthesia with LMA insertion	- Severity of sore throat - Hoarseness - Dysphagia (rated on four-point categorical scales)
Prospective, randomized, single-blinded, controlled trial comparing the effectiveness of a sea salt/glycerine spray, flurbiprofen 8.75 mg lozenges, and a stomatitis/gingivitis gargle in alleviating POST after endotracheal intubation					
Aydin, J Anesth 2014 ⁴⁰	Lozenge	Flurbiprofen (n=80) 10 mg sea salt/glycerine spray (n=80) Stomatitis/gingivitis gargle (n=80) No treatment (n=80)	Single dose, 45 min before induction of anesthesia (24 h)	Patients undergoing elective genitourinary surgery under general orotracheal anesthesia	Incidence and severity of POST

Notes: *Combined data from NCT01048866 and NCT01049334.

Abbreviations: CLIN, Practitioner's Clinical Assessment of Drug Efficacy; DSS, Difficulty Swallowing Scale; GLOBAL, patient's global evaluation of study treatment; LMA, laryngeal mask airway; POST, post-operative sore throat; QuaSTI, Qualities of Sore Throat Index; SATIS, satisfaction scale; SPID, summed difference in sore throat pain intensity; STPIS, Sore Throat Pain Intensity Scale; STRRS, Sore Throat Relief Rating Scale; STS, Sore Throat Scale; SwoTS, Swollen Throat Scale; TOTPAR, sum of total pain relief scores; TPS, Throat Pain Scale; TSS, Throat Soreness Scale; URTI, upper respiratory tract infection.

With regard to relief of sore throat (as measured on the STRRS), Schachtel et al¹⁷ reported significantly greater relief with flurbiprofen lozenge vs placebo at all time points from 1–4 h (all $p < 0.05$). Burova et al²⁵ observed that 74–78% of patients experienced “at least moderate relief” by 2 h post-dose with flurbiprofen lozenge or spray, and 98% experienced “slight” relief over the same period. In the study by Schachtel et al,¹⁷ the sum of total pain relief scores (TOTPAR), calculated from the STRRS, was 82% greater with flurbiprofen lozenge compared with placebo over the 1–2 h post-dose period ($p < 0.001$), with 53% of patients taking flurbiprofen experiencing “at least moderate relief” (compared with 26% of placebo patients; $p < 0.001$). Several other studies have also reported significantly greater improvements in sore throat relief with single-dose flurbiprofen (lozenges, spray or microgranules) vs placebo for between 2 and 6 hrs post-dose.^{32,34,38}

Radkova et al²⁶ and Burova et al²⁵ reported similar efficacy of single-dose flurbiprofen spray and lozenge for sore throat relief. One paper, by Watson et al,²² failed to demonstrate a significant improvement in TOTPAR over 2 h vs placebo, although a trend in favor of flurbiprofen lozenge was observed ($p = 0.06$). However, analysis of sore

throat relief at individual time points revealed significant differences in favor of flurbiprofen compared with placebo at 45, 60, and 75 min ($p < 0.05$).

Significant reductions in throat soreness (as measured on the TSS and STS) have also been observed with single-dose flurbiprofen across all studies reporting these measures, ranging from 23% to 124% greater reductions in throat soreness vs placebo over 2 h, where numerical data are reported.^{22,28,31,32,34,38}

Multiple Dose

Eight of the papers have provided clinical evidence that multiple-dose flurbiprofen, taken every 3–6 h as needed (up to 5 or 8 doses in 24 h), provide continued relief from sore throat pain and soreness;^{22,29–31,34,36–38} six for flurbiprofen lozenges, one for spray, and one for microgranules. Several of the papers evaluated pain relief during the first 24 h of treatment, when throat symptoms are most prominent and often require repeated treatment.^{29,30,36,37} All of these papers reported significant reductions in sore throat pain (up to 80% greater compared to placebo; measured on the STPIS) over this treatment period.^{29,30,36,37} Five papers explored the efficacy of repeated self-dosing of

Table 2 Summary of Key Assessment Tools Used in the Included Studies

Assessment Tool	Description
Sore Throat Pain Intensity Scale (STPIS) ⁴⁶	100 mm VAS: 0 = no pain, 100 = severe pain
Sore Throat Scale (STS) ²⁷	11-point ordinal scale: 0 = not sore, 10 = very sore
Throat Soreness Scale (TSS) ³⁴	11-point ordinal scale: 0 = not sore to 10 = very sore
Throat Pain Scale (TPS) ³⁴	4-point categorical scale: no, mild, moderate or severe pain
Sore Throat Relief Rating Scale (STRRS) ³⁴	7-point categorical scale: no, slight, mild, moderate, considerable, almost complete and complete relief
Swollen Throat Scale (SwoTS) ⁴⁷	100 mm VAS: 0 = not swollen, 100 = very swollen
Difficulty Swallowing Scale (DSS) ⁴⁷	100 mm VAS: 0 = not difficult, 100 = very difficult
Qualities of Sore Throat Index (QuaSTI) ²⁸	A validated 11-item composite index comprised of the STS score plus 10 other qualities of sore throat (burning, raw, dry, husky/hoarse voice, irritated/scratchy [factor 1]; like a lump in the throat, tight, difficulty swallowing, swollen, soreness [factor 2]; and agonizing [factor 3]) assessed on 0–10 Likert scales
Upper respiratory tract infection (URTI) questionnaire ²⁸	Questionnaire describing the presence/absence of 39 different symptoms of URTI
Double stopwatch (DSW) method for onset of analgesic action ³⁵	Subjects are instructed to depress a first stopwatch when they perceive any pain relief and a second when they experience what they consider to be 'meaningful' pain relief
Patient's global evaluation of the study treatment (GLOBAL) ³⁴	5-point categorical scale: poor, fair, good, very good, excellent
Patient satisfaction scale (SATIS) ³⁴	7-point categorical scale: extremely dissatisfied, very dissatisfied, dissatisfied, somewhat satisfied, satisfied, very satisfied, extremely satisfied
Overall treatment rating scale ²²	11-point ordinal subjective scale: 0 = poor, 10 = excellent

Abbreviation: VAS, visual analogue scale.

flurbiprofen beyond the first 24 h. Schachtel et al³⁶ observed that multiple-dose flurbiprofen lozenge over days 2–7 continued to provide significant reductions in sore throat pain intensity from before to 2 h after each dose, and that flurbiprofen provided 74% greater reduction in sore throat pain intensity vs placebo over days 2–7 ($p<0.01$). Likewise, de Looze et al³⁴ reported that multiple-dose flurbiprofen spray provided a greater reduction in severity of throat soreness and pain intensity, and significantly greater sore throat relief compared with placebo, up to the end of the 3-day study period ($p<0.05$).

Blagden et al³¹ demonstrated the superiority of flurbiprofen vs placebo in relieving sore throat over days 1–4 overall (TOTPAR at the end of days 1–4; $p=0.0113$). However, in a subgroup of patients not prescribed concomitant antibiotics in this study, significance was reached on days 2 and 3 ($p<0.05$), but not on day 1 ($p=0.06$) and day 4 ($p=0.09$). In terms of change from baseline in sore throat relief, significance was achieved with multiple-dose flurbiprofen

microgranules vs placebo at the end of day 1 ($p=0.026$), but not at the end of day 2 ($p=0.101$) and day 3 ($p=0.078$).³⁸

Severe Sore Throat

In a study by Aspley et al,²⁹ the efficacy of flurbiprofen lozenge was evaluated in a subgroup of patients with relatively severe sore throat pain (baseline STPIS score of >80.5 mm). In these patients, multiple-dose flurbiprofen provided 135.7% greater (269.9 mm*h; 95% CI: 84.7, 455.1) reduction in pain intensity than placebo-treated patients ($p<0.01$) over 24 h. Improvement of sore throat pain after single-dose flurbiprofen was similar for patients with relatively severe symptoms and the overall study population, with onset differentiated between flurbiprofen and placebo beginning at approximately 30–40 min through to 3 h ($p<0.05$). Moreover, Schachtel et al³⁵ reported that pain reduction was achieved by 95% of flurbiprofen-treated patients over 3 h (vs 63% of placebo-treated patients; $p=0.02$) in a subgroup of patients (42%) with more severe

Table 3 Summary of Studies Reporting Throat Pain and Soreness Outcomes^a

Reference	Outcome Measure (Units)	Baseline Score Mean (±SD)	Post Intervention Mean (±SD, if Reported)	Summary of Key Outcomes
Randomized, double-blind, single-dose, placebo-controlled, single-center study to assess the efficacy of flurbiprofen 8.75 mg lozenges in patients with acute sore throat (NCT01986361)				
Schachtel, Pain Manag 2018 ²⁸	STS (mm)	Flurbiprofen lozenge (n=101): 7.4 (0.97) Placebo (n=21): 7.3 (1.02)	NR	Single dose Patients using flurbiprofen consistently reported a significant reduction in throat soreness at 1, 2, and 3 h (all p<0.01)
Schachtel, Br J Pain 2018 ³⁵	STPIS (mm)	Flurbiprofen lozenge (n=101): 73.8 (9.8) Placebo (n=21): 73.8 (9.6)	NR	Single dose First perceived pain relief ^b 97% of flurbiprofen- and 76% of placebo-treated patients reported pain relief over the 3 h study period (p<0.01) 85% of flurbiprofen patients reported pain relief within 30 min and 97% within 60 min, compared with 67% and 76% of placebo-treated patients, respectively Meaningful pain relief ^c 78% of flurbiprofen- and 48% of placebo-treated patients had meaningful pain relief over the 3 h study period (p<0.01) 32% of flurbiprofen patients reported meaningful relief within 30 min and 66% within 60 min, compared with 19% and 43% of placebo-treated patients, respectively
Randomized, double-blind, placebo-controlled, multiple-dose, single-center, parallel-group study of the efficacy of flurbiprofen 8.75 mg lozenges compared with placebo lozenges in adult patients with acute sore throat (NCT01049334)				
Schachtel, Pain 2014 ¹⁷	STPIS (mm)	Flurbiprofen lozenge (n=102): 78.8 (8.56) Placebo (n=102): 80.5 (7.92)	SPID over 2 h (mm ⁴ h) - Flurbiprofen (n=102): -43.4 (39.20) - Placebo (n=102): -23.5 (29.52)	Single dose - Reduction in pain intensity was significantly greater (85%) with flurbiprofen vs placebo over 2 h (p<0.001) - A 46% mean peak reduction in pain intensity was reported with flurbiprofen compared with 33% for placebo (p<0.001), and greater absolute reduction of pain than placebo (p<0.05) for up to 4 h
	STRS (mm)	NA	Total pain relief over 2 h - Flurbiprofen (n=102): 3.1 (1.85) - Placebo (n=102): 1.7 (1.77)	Single dose - Total pain relief was significantly greater (82%) with flurbiprofen vs placebo over 2 h (p<0.001) - Moderate or greater pain relief was experienced within 2 h by 53% of flurbiprofen patients compared with 26% of placebo patients (p<0.001) - Flurbiprofen-treated patients reported 56% greater mean peak relief than placebo (p<0.001) - Significant differences were observed between flurbiprofen and placebo at the 1 h assessment point and for up to 4 h (p<0.05)
Aspley, Curr Med Res Opin 2016 ²⁹	STPIS (mm)	Flurbiprofen lozenge (n=59): 79.7 (9.12) Placebo (n=65): 80.3 (7.86)	SPID over 24 h (mm ⁴ h) - Flurbiprofen (n=58): -477.8 - Placebo (n=65): -265.7	Single dose - Flurbiprofen provided significantly greater reduction in pain intensity vs placebo from 22 min through to 210 min (p<0.05) - Similar reduction in pain intensity with flurbiprofen vs placebo in patients with relatively severe symptoms from 24–26 min and from 32–180 min (p<0.05) Multiple dose - Significantly greater reduction (80%) of pain with flurbiprofen than with placebo (p<0.01; 95% CI: 60.7, 363.7) over 24 h - Significantly greater reduction (136%) of pain with flurbiprofen than with placebo (p<0.01; 95% CI: 84.7, 455.1) in patients with relatively severe pain over 24 h

Schachtel, Pain Manag 2016 ³⁶	STPIS (mm)	Flurbiprofen lozenge (n=102): 78.8 (8.56) Placebo (n=102): 80.5 (7.92)	SPID over 24 h (mm ⁴ h) ● Flurbiprofen (n=101): -473.7 ● Placebo (n=100): -322.3 Difference from pre-dose to 2 h post-dose in STPIS (LS mean scores) over days 2-7 (mm) ● Flurbiprofen (n=94): -13.9 ● Placebo (n=96): -8.0	Multiple dose ● Significantly greater reduction (47%) of pain intensity with flurbiprofen compared with placebo over 24 h (p=0.02; LS mean difference of -151.5; 95% CI: -278.9, -24.0) ● Flurbiprofen provided significantly greater (74%) mean relief of pain vs placebo over 2-7 days (p<0.01; LS mean difference of -5.9 mm; 95%CI: -9.8, -2.1)
Shepherd, Int J Clin Pract 2015 ^{37d}	STPIS (mm)	Flurbiprofen lozenge (n=203): 78.9 (8.3) Placebo (n=199): 79.8 (8.2)	NR	Single dose ● Flurbiprofen provided significantly greater reduction in sore throat pain vs placebo in the entire population for up to 4 h (p<0.01) Multiple dose ● For the SPID over 24 h, the differences were greater for flurbiprofen vs placebo in the entire population (52.1% more relief; p<0.001)
Randomized, double-blind, placebo-controlled, parallel-group study to examine the efficacy and safety of multiple doses of flurbiprofen 8.75 mg lozenge, with a focus on the initial 24 h of treatment (NCT01048866)				
Schachtel, Trials 2014 ³⁰ 2015 ^{37d}	STPIS (mm)	Flurbiprofen lozenge (n=101): 79.1 (8.1) Placebo (n=97): 79.1 (8.4)	SPID over 24 h (mm ⁴ h) ● Flurbiprofen (n=99): -529.2 ● Placebo (n=95): -332.6	Single dose ● A statistically significant reduction in sore throat pain intensity was observed with flurbiprofen vs placebo up to 3 h post-dose (p<0.01) Multiple dose ● Significantly greater reduction (59%) of pain with flurbiprofen vs placebo over 24 h (p<0.01; difference of -196.6 mm ⁴ h; 95%CI: -321.0, -72.2) ● Significantly more patients reported ≥20% reduction in sore throat pain intensity with flurbiprofen vs placebo (61.4 and 37.1% respectively; p<0.001) ● Flurbiprofen provided 38% greater mean relief of pain vs placebo (p<0.07; difference of -8.2 mm; 95%CI: -17.1, 0.7) over 2-7 days
Randomized, double-blind, parallel-group, placebo-controlled, multicenter study to assess the efficacy and safety of flurbiprofen 8.75 mg lozenges in patients with sore throat in UK general practice				
Blagden, Int J Clin Pract 2002 ³¹	STRRS	NA	TOTPAR over days 1-4 ● Flurbiprofen lozenge (n=184): 12.4 (0.4) ● Placebo (n=179): 11.1 (0.4)	Multiple dose ● Flurbiprofen was significantly superior to placebo in relieving sore throat pain at the end of days 1-4 (TOTPAR _{days 1-4} difference of -1.3; p=0.0113)
	TSS	Flurbiprofen lozenge (n=230): 7.6 (1.3) Placebo (n=229): 7.6 (1.2)	Mean sum of changes from baseline in TSS at 2 h ● Flurbiprofen (n=192): -1.01 (0.1) ● Placebo (n=182): -0.45 (0.1) Mean sum of changes from baseline in TSS over days 1-4 ● Flurbiprofen (n=184): -12.6 (0.6) ● Placebo (n=181): -11.1 (0.6)	Single dose ● Mean change from baseline in throat soreness was significantly greater (124%) with flurbiprofen compared with placebo at 2 h (p<0.001) Multiple dose ● Mean change from baseline in throat soreness was significantly greater with flurbiprofen compared with placebo at 1 day (p=0.0016) ● The difference in mean sum of changes from baseline in throat soreness over days 1-4 between flurbiprofen and placebo trended towards significance (p=0.057) ● 49% of flurbiprofen patients achieved a ≥1-point reduction in TSS score vs 31.3% of placebo patients

(Continued)

Table 3 (Continued).

Reference	Outcome Measure (Units)	Baseline Score Mean (±SD)	Post Intervention Mean (±SD, if Reported)	Summary of Key Outcomes
Randomized, double-blind, parallel-group, single-center study comparing the efficacy and tolerability of flurbiprofen lozenges (8.75 mg or 12.5 mg) with placebo in the treatment of patients with sore throat due to upper respiratory tract infection				
Benrimoj, Clin Drug Investig 2001 ³²	STRRS	NA	TOTPAR over 15–120 min ● Flurbiprofen lozenge (n=120): 17.9 (0.9) ● Placebo (n=125): 15.6 (0.9)	Single dose ● Flurbiprofen was significantly superior to placebo (15% greater) in relieving sore throat pain at the end of 15–120 min (TOTPAR _{15–120 min} difference of -2.3; p=0.037), with a statistically significant difference between the two groups being clearly seen after 45 min (p<0.05)
	TSS	Flurbiprofen lozenge (n=128): 7.4 (1.0) Placebo (n=128): 7.5 (1.0)	Sum of change from baseline in TSS over 15–120 min ● Flurbiprofen (n=120): -15.3 (1.0) ● Placebo (n=125): -12.4 (0.9)	Single dose ● Flurbiprofen was associated with a significantly greater (23%) reduction in throat soreness vs placebo over 2 h (difference of -2.9; p=0.019) and showed a trend towards significance over 6 h (difference of -3.7; p=0.058)
Randomized, double-blind, parallel-group, placebo-controlled, single- and multiple-dose, single-center study to assess the efficacy and safety of flurbiprofen 8.75 mg and 12.5 mg lozenges in patients with relatively severe sore throat due to upper respiratory tract infection				
Watson, Int J Clin Pract 2000 ²²	STRRS	NA	TOTPAR over 15–120 min ● Flurbiprofen lozenge (n=128): 12.68 (0.8) ● Placebo (n=128): 10.47 (0.8)	Single dose ● Flurbiprofen was not significantly superior to placebo in relieving sore throat pain at the end of 15–120 min (mean TOTPAR _{15–120 min} difference of -2.21; p=0.06) or 15–360 min (p=0.068), although a trend in favor of flurbiprofen was observed ● Analysis of pain relief at individual time points revealed significant differences between flurbiprofen and placebo at 45, 60 and 75 min (p=0.014, p=0.035 and p=0.042, respectively) Multiple dose ● Flurbiprofen was significantly better than placebo in providing pain relief on days 2 (p=0.004), 3 (p=0.011) and 4 (p=0.003)
	TSS	Flurbiprofen lozenge (n=129): 7.03 (0.91) Placebo (n=129): 6.94 (0.85)	Sum of change from baseline in TSS over 15–120 min ● Flurbiprofen (n=126): -9.94 (0.8) ● Placebo (n=128): -6.93 (0.7)	Single dose ● Flurbiprofen was associated with a significantly greater (45%) reduction in throat soreness vs placebo over 2 h (difference of -3.01; p=0.008) and over 3 h (difference of -4.13; p=0.021) Multiple dose ● Flurbiprofen was significantly better than placebo in reducing throat soreness on days 2 (p=0.037), 3 (p=0.005) and 4 (p=0.0003)
Randomized, double-blind study, placebo-controlled, parallel-group study to assess the efficacy of flurbiprofen 8.75 mg spray in adults with sore throat due to upper respiratory tract infection (ACTRNI 2612000457842)				
de Looze, Eur J Gen Pract 2016 ³⁴	STPIS (mm)	Flurbiprofen spray (n=249): 67.75 (11.02) Placebo (n=256): 69.11 (9.97)	NR	Single dose ● The SPID at 2, 3 and 6 h were significantly superior with flurbiprofen vs placebo (p<0.0001) ● Change in sore throat pain intensity was significantly greater with flurbiprofen from 20 min (p<0.01) for up to 6 h, vs placebo Multiple dose ● Flurbiprofen provided a greater reduction in the change from baseline in sore throat pain intensity at the end of day 1, at 24 h (±15 min), and at the end of days 2 and 3 vs placebo (p<0.05 for all)

	TSS	Flurbiprofen spray (n=249): 6.93 (0.90) Placebo (n=256): 6.99 (0.84)	AUC for throat soreness from 0–2 h ● Flurbiprofen (n=249): -1.82 (1.35) ● Placebo (n=256): -1.13 (1.14)	Single dose - The AUC for throat soreness was significantly greater (61%) with flurbiprofen compared with placebo at 2 h (LS means difference -0.70; 95% CI: -0.91, -0.48; p<0.0001). Similar results were observed at 3 and 6 h (p<0.0001) - The change from baseline in severity of throat soreness was significantly greater with flurbiprofen vs placebo from 5 min (first time point), and at each subsequent time point until 6 h (p<0.01 for all) Multiple dose - Flurbiprofen provided a greater reduction in the change from baseline in the severity of throat soreness at the end of day 1, at 24 h (±15 min), and at the end of days 2 and 3 vs placebo (p<0.05 for all)
	STRRS	NA	NR	Single dose - The TOTPAR scores at 2, 3 and 6 h were significantly superior with flurbiprofen vs placebo (p<0.0001) - During the 6 h post-first dose, (55.0%) of patients reported at least 30 min of "moderate" sore throat relief with flurbiprofen vs 34.8% receiving placebo (p<0.001) Multiple dose - Flurbiprofen provided significantly greater sore throat relief, at the end of day 1, at 24 h (±15 min), and at the end of days 2 and 3 vs placebo (p<0.05 for all)
	TPS	NR	NR	At 2, 3 and 6 h, and the final visit, fewer patients reported their throat pain as "moderate-to-severe" with flurbiprofen vs placebo (p<0.01 for 2, 3 and 6 h; p<0.319 for final visit)
de Looze, Pain Manag 2018 ³³	STRRS	NA	NR	Single dose - Mean sore throat relief was consistently greater for flurbiprofen spray vs placebo after the first dose - Mean TOTPAR ratings up to 6 h after the first dose were significantly greater for flurbiprofen spray vs placebo: 3.24 (95% CI: 3.06, 3.42) compared with 2.47 (95% CI: 2.32, 2.63; p<0.0001) - Significantly more patients reported at least 30 min of "at least moderate" relief over 6 h post-dose with flurbiprofen spray vs placebo (55% vs 34.8%; p<0.0001)
Multicenter, double-blind, double-dummy, non-inferiority study to assess the efficacy of flurbiprofen 8.75 mg delivered as a spray or lozenge in patients with sore throat due to upper respiratory tract infection				
Radkova, J Pain Res 2017 ²⁶	STPIS (mm)	Flurbiprofen spray (n=205): 78.9 (7.78) Flurbiprofen lozenge (n=212): 79.4 (7.68)	SPID over 2 h ● Flurbiprofen spray (n=205): -40.7 (21.64) ● Flurbiprofen lozenge (n=212): -40.3 (22.27)	Single dose - Mean reductions in sore throat pain intensity from baseline to 2 h post-dose (SPID_{2h}) were similar for flurbiprofen spray (LS mean -40.51) and flurbiprofen lozenge (LS mean -40.10) (LS means difference 0.41; 95% CI: -3.20, 4.01; p=0.82) - There was no significant difference between spray and lozenge in SPID_{1hr} or SPID_{2h}
Burova, J Pain Res 2018 ²⁵	STRRS	NA	NR	Single dose - TOTPAR over 2 h post-dose was similar for flurbiprofen spray (n=205) (2.55; 95% CI: 2.29, 2.81) and flurbiprofen lozenge (n=212) (2.57; 95% CI: 2.31, 2.84); the LS means difference between treatments was not statistically significant (p=0.7305) - Overall, 98% of patients experienced at least 'slight' relief (≥1 on the STRRS) and 76% at least 'moderate' relief by 2 h
Randomized, double-blind, placebo-controlled, multiple-dose, multicenter study to determine the analgesic efficacy of flurbiprofen 8.75 mg microgranules vs placebo for patients with sore throat due to upper respiratory tract infection				

(Continued)

Table 3 (Continued).

Reference	Outcome Measure (Units)	Baseline Score Mean (±SD)	Post Intervention Mean (±SD, if Reported)	Summary of Key Outcomes
Russo, Br J Gen Pract 2013 ³⁸	TSS	Flurbiprofen microgranules (n=186): 6.78 (0.78) Placebo (n=187): 6.73 (0.87)	AUC for throat soreness from 0–2 h ● Flurbiprofen (n=186): -2.14 (1.74) ● Placebo (n=187): -1.65 (1.67)	Single dose ● Significantly greater (30%) reduction in throat soreness over the first 2 h with flurbiprofen vs placebo (LS means difference -0.48; 95% CI: -0.81, -0.15; p=0.0049) ● The mean change from baseline in throat soreness was significantly greater with flurbiprofen vs placebo at all time points up to 300 min post-dose (p<0.05) ● The difference in AUC from baseline to 3 and 6 h for throat soreness was significant with flurbiprofen vs placebo (p=0.0035 and p=0.0051, respectively)
	STPIS (mm)	NR	NR	Single dose ● The mean change in sore throat pain intensity was significantly greater for flurbiprofen vs placebo at all time points (p<0.05), apart from 1, 15, 30, and 45 min post-dose
	STRRS	NA	NR	Single dose ● AUC analyses also showed a significant difference with flurbiprofen at 3 and 6 h (p=0.0020 and p=0.0043, respectively) Multiple dose ● Sore throat relief was significantly higher with flurbiprofen vs placebo at 24 h (LS means difference 0.42; 95% CI: 0.05, 0.80; p=0.026) and favored flurbiprofen at the end of days 2 and 3 (NS)

Notes: ^aWhere more than one dose of flurbiprofen was studied, only data for the 8.75 mg dose are included. ^bPatients were instructed to depress a first stopwatch when they first perceived any pain relief. ^cPatients were instructed to depress a second stopwatch when they experienced relief that was meaningful to them. ^dCombined data from NCT01048866 and NCT01049334.
Abbreviations: AUC, area under the change from baseline curve; LS, least square; NA, not applicable; NR, full data not reported; NS, not significant; SPID, Summed Pain Intensity Difference; STPIS, Sore Throat Pain Intensity Scale; STRRS, Sore Throat Relief Rating Scale; STS, Sore Throat Scale; TOTPAR, sum of total pain relief scores; TSS, Throat Soreness Scale.

sore throat pain at baseline (STS score >7 and Tonsillo-Pharyngitis Assessment [TPA] score >7).

Meaningful Pain Relief

Determining a reduction in pain that is clinically important, or meaningful to patients, may offer more interpretable results with direct clinical implications.⁴⁴ Several of the studies included in this review have assessed “meaningful” pain relief with flurbiprofen.^{17,18,33,35} Using a double stopwatch (DSW) method (Table 2), Schachtel et al³⁵ investigated both “first perceived” pain relief (the moment the patient experiences any pain relief, measured on the STPIS) and “meaningful” pain relief (when the patient experiences relief that is meaningful to them) with flurbiprofen lozenge. Results showed that 97% of flurbiprofen-treated patients ($n=101$) experienced “first perceived” pain relief, with 78% achieving “meaningful” analgesia within the 3 h study period. In contrast, although 76% of patients taking placebo lozenge ($n=21$) reported “first perceived” pain relief over the 3 h study period, the relief was not considered “meaningful” in over half of patients (52%). “Meaningful” pain relief was achieved by 32% (32/101) of flurbiprofen-treated patients within 30 min and by 66% (67/101) within 60 min – compared with 19% (4/21) and 43% (9/21) of placebo-treated patients, respectively. A subgroup analysis also demonstrated significant efficacy of flurbiprofen in patients with more severe sore throat; in these patients, “meaningful” relief was reported by 70% of flurbiprofen-treated patients and 13% of placebo-treated patients ($p<0.01$).

Meaningful pain relief was also assessed by Schachtel et al¹⁷ in another study using the established criteria of “at least moderate relief” of acute pain to define a clinically important effect size. Sore throat pain was assessed at frequent (2 min) intervals on the STPIS, and onset of pharmacological activity was defined as the median time of “first perceived” pain reduction if a patient reported clinically meaningful “at least moderate” relief. Patients receiving a single flurbiprofen lozenge first reported “meaningful” pain relief at 12 min, with a significant differentiation from placebo in terms of percentage reduction in pain intensity (indicative of change relative to each individual patient’s pretreatment pain intensity) beginning at 26 min (24% pain reduction with flurbiprofen vs 16% with placebo; $p<0.05$).

The previous findings were confirmed with flurbiprofen spray in a study by de Looze et al.³³ Patients were required to report at least 30 min of “at least moderate” sore throat

relief on the STRRS for the relief to be regarded as “clinically meaningful”. Significantly more patients using flurbiprofen spray reported at least 30 min of “at least moderate” relief than those using placebo during the 6 h after a single dose (55% vs 35%, respectively; OR: 2.31; 95% CI: 1.61, 3.62; $p<0.0001$), and this was achieved more quickly with flurbiprofen than placebo (HR: 1.96; 95% CI: 1.50, 2.57; $p<0.0001$); 150 min for flurbiprofen and not calculated for placebo due to less than 50% response. Sore throat severity was reduced by at least 2.2 mm on the STS from 75 min to 6 h post dosing, indicating “meaningful relief”.

Difficulty Swallowing

Eleven of the papers reviewed reported data evaluating the efficacy of flurbiprofen in reducing difficulty swallowing (Table 4) – a common symptom associated with inflammation of the throat, usually measured on the Difficulty Swallowing Scale (DSS; Table 2). Significantly greater improvements in swallowing have been observed from 5 min after taking single-dose flurbiprofen compared with placebo,³⁴ and for up to 6 h post-dose.³⁴ The superior efficacy of flurbiprofen in reducing difficulty swallowing has also been demonstrated with repeated dosing. Aspley et al²⁹ observed a 99.6% greater reduction in difficulty swallowing with multiple-dose flurbiprofen lozenges compared with placebo over 24 h ($p<0.01$), and an even greater reduction (105.4%) in patients who had relatively severe difficulty swallowing (baseline DSS score >77.5 mm). Furthermore, significantly greater improvements in swallowing have been reported for longer treatment periods of up to 7 days compared with placebo.^{29–31,34,36–38}

Sensation of Swollen Throat

Eleven of the papers reported data evaluating the efficacy of flurbiprofen in reducing the sensation of swollen throat (Table 5), commonly assessed on the Swollen Throat Scale (SwoTS; Table 2). As with the other symptoms associated with sore throat, the data generally support that flurbiprofen is effective at reducing the sensation of swollen throat rapidly after a single dose – with significantly greater reductions observed from 30 min to up to 6 h post-dose^{17,25,30,32,34,37} – and after multiple dosing over 1–7 days.^{22,29,30,34,36,37} Notably, Aspley et al²⁹ observed a 69.3% greater reduction in sensation of swollen throat with multiple-dose flurbiprofen lozenges compared with placebo over 24 h ($p<0.05$), and an even greater reduction (148.6%) in patients who had relatively severe symptoms (baseline SwoTS score >81.5 mm).

Table 4 Summary of Studies Reporting Difficulty Swallowing Outcomes^a

References	Outcome Measure	Baseline Score Mean (SD)	Endpoint	Outcomes
Randomized, double-blind, single-dose, placebo-controlled, single-center study to assess the efficacy of flurbiprofen 8.75 mg lozenges in patients with acute sore throat (NCT01986361)				
Schachtel, Pain Manag 2018 ²⁸	QuaSTI (difficulty swallowing)	Flurbiprofen lozenge (n=101): 8.0 (1.47) Placebo (n=21): 7.6 (2.09)	NR	Single dose Patients using flurbiprofen reported significant reductions of scores from baseline in difficulty swallowing at 1, 2 and 3 h (all p<0.01)
Randomized, double-blind, placebo-controlled, multiple-dose, single-center, parallel-group study of the efficacy of flurbiprofen 8.75 mg lozenges compared with placebo lozenges in adult patients with acute sore throat (NCT01049334)				
Schachtel, Pain 2014 ¹⁷	DSS (mm)	Flurbiprofen lozenge (n=102): 76.9 (12.41) Placebo (n=102): 76.3 (11.04)	NR	Single dose - Patients using flurbiprofen reported progressively greater absolute and percentage reductions in DSS vs patients using placebo - Reduction in difficulty swallowing was perceived at the first post-treatment assessment time point (10 min) by patients sucking flurbiprofen or placebo - By 20 min, there was a 19% DSS reduction with flurbiprofen vs 10% with placebo (p<0.01) - At 2 h, patients treated with flurbiprofen reported a 27% reduction in difficulty swallowing, vs 9% reduction by patients on placebo (p<0.001) - Flurbiprofen-treated patients reported a 44% mean peak reduction of difficulty swallowing, vs 27% for placebo (p<0.001) - The summed difference in difficulty swallowing over 2 h also differentiated flurbiprofen from placebo (mean $\pm$SD, -39.1 $\pm$ 38.64 mm³h with flurbiprofen, -16.6 $\pm$ 29.34 mm³h with placebo, p<0.001) - Flurbiprofen was associated with significantly greater absolute and percentage reductions in DSS score vs placebo for up to 4 h (both p<0.05)
Aspley, Curr Med Res Opin 2016 ²⁹	DSS (mm)	Flurbiprofen lozenge (n=59): 77.9 (12.29) Placebo (n=65): 76.0 (11.59)	Summed reduction in DSS score (LS mean) over 24 h (mm ³ h) - Flurbiprofen (n=58): 441.0 - Placebo (n=65): 220.9	Single dose - Flurbiprofen provided significantly greater reduction in difficulty swallowing vs placebo from 10 min through to 210 min (p<0.05) - Onset of relief from difficulty swallowing was differentiated between flurbiprofen and placebo from 40 to 180 min (p<0.05) Multiple dose 99.6% greater reduction of difficulty swallowing with flurbiprofen vs placebo (difference of 220.2 mm³h; 95% CI: 53.8, 386.5; p<0.01) over 24 h - For patients who had relatively severe difficulty swallowing (baseline DSS score >77.5 mm), flurbiprofen provided 105.4% greater improvement in swallowing than placebo (difference of 266.2 mm³h; 95% CI: 71.4, 460.9; p<0.01) over 24 h

Schachtel, Pain Manag 2016 ³⁶	DSS (mm)	Flurbiprofen lozenge (n=102): 76.9 (12.41) Placebo (n=102): 76.3 (11.04)	Summed difference in DSS scores (LS mean) over 24 h (mm ^{3h}) ● Flurbiprofen (n=101): -458.4 ● Placebo (n=99): -276.7 Difference in DSS score from pre-dose to 2 h post-dose (LS means) over 2-7 days (mm) ● Flurbiprofen (n=94): -14.1 ● Placebo (n=96): -8.2	Multiple dose ● 66% greater improvement in swallowing with flurbiprofen vs placebo (difference of -181.7 mm^{3h}; 95% CI: -313.3, -50.0; p<0.01) over 24 h ● Subsequent uses of flurbiprofen (over 2-7 days) provided 72% greater improvement in swallowing vs placebo (difference of -5.9 mm; 95% CI: -9.7, -2.1; p<0.01)
Shepherd, Int J Clin Pract 2015 ^{37b}	DSS (mm)	Flurbiprofen lozenge (n=203): 77.4 (11.5) Placebo (n=199): 77.2 (10.8)	NR	Single dose ● Flurbiprofen provided significantly greater reduction in difficulty swallowing vs placebo for the entire population at 1, 2 and 3 h (all p<0.001) and at 4 h (p<0.01) Multiple dose ● Flurbiprofen over 24 h provided 48.9% greater relief of difficulty swallowing vs placebo in the entire population (p<0.0001)
Randomized, double-blind, placebo-controlled, parallel-group study to examine the efficacy and safety of multiple doses of flurbiprofen 8.75 mg lozenge, with a focus on the initial 24 h of treatment (NCT01048866)				
Schachtel, Trials 2014 ³⁰	DSS (mm)	Flurbiprofen lozenge (n=101): 77.9 (10.6) Placebo (n=97): 78.2 (10.4)	Summed difference in DSS scores (LS mean) over 24 h (mm ^{3h}) ● Flurbiprofen (n=99): -575.6 ● Placebo (n=95): -395.9	Single dose ● Reductions in absolute DSS scores were observed at each hourly assessment up to and including 4 h post-dose with flurbiprofen vs placebo (p<0.05) ● Significantly more patients reported ≥20% reduction in difficulty swallowing with flurbiprofen vs placebo (57.4 and 36.1%, respectively; p<0.01) Multiple dose ● 45% greater relief of difficulty swallowing with multiple doses of flurbiprofen vs placebo (difference of -179.7 mm^{3h}; 95% CI: -305.7, -53.8; p<0.01) over 24 h ● Patients taking flurbiprofen over days 2-7 experienced a 36.9% greater improvement in difficulty swallowing (difference of -7.5 mm; 95% CI: -16.2, 1.3; p=0.09) vs placebo

(Continued)

Table 4 (Continued).

References	Outcome Measure	Baseline Score Mean (SD)	Endpoint	Outcomes
Randomized, double-blind, parallel-group, placebo-controlled, multiple-dose, multicenter study to assess the efficacy and safety of flurbiprofen 8.75 mg lozenges in patients with sore throat in UK general practice				
Blagden, Int J Clin Pract 2002 ³¹	DSS (mm)	Flurbiprofen lozenge (n=230): 66.5 (19.3) Placebo (n=229): 64.7 (18.7)	Mean sum of changes from baseline in DSS at 2 h ● Flurbiprofen (n=192): -8.41 (1.03) ● Placebo (n=182): -3.46 (0.68) Mean sum of changes from baseline in DSS over days 1-4 ● Flurbiprofen (n=187): -107.8 (5.9) ● Placebo (n=178): -89.6 (5.9)	Single dose ● The mean sum of changes in DSS from baseline was significantly greater with flurbiprofen at 2 h compared with placebo (p<0.001) ● Significant differences in mean change from baseline between flurbiprofen and placebo occurred at the 2 h time point (p=0.0001) Multiple dose ● The mean sum of changes of DSS was significantly greater with flurbiprofen over 1-4 days compared with placebo (p<0.05) ● Significant differences in mean change from baseline between flurbiprofen and placebo occurred at day 1 (p=0.0001)
Randomized, double-blind, placebo-controlled, parallel-group study to assess the efficacy of flurbiprofen 8.75 mg spray in adults with sore throat due to upper respiratory tract infection (ACTRN12612000457842)				
de Looze, Eur J Gen Pract 2016 ³⁴	DSS (mm)	Flurbiprofen spray (n=249): 68.60 (10.91) Placebo (n=256): 69.66 (10.21)	NR	Single dose ● Significantly greater change from baseline in DSS with flurbiprofen at 2, 3, and 6 h vs placebo (p<0.0001) ● Change in difficulty swallowing was significantly greater with flurbiprofen spray from 5 min (p<0.05) for up to 6 h, vs placebo Multiple dose ● Flurbiprofen provided a greater reduction in difficulty swallowing at the end of day 1, at 24 h (±15 min), and at the end of days 2 and 3 (p<0.05 for all) vs placebo

Multicenter, double-blind, double-dummy, non-inferiority study to assess the efficacy of flurbiprofen 8.75 mg delivered as a spray or lozenge in patients with sore throat due to upper respiratory tract infection				
Burova, J Pain Res 2018 ²⁵	DSS (mm)	Flurbiprofen spray (n=217): 69.3 (13.01) Flurbiprofen lozenge (n=222): 70.9 (11.27)	Change from baseline in DSS (LS mean) at 1 h - Flurbiprofen spray (n=205): –33.39 (95% CI: –38.46, –28.32) - Flurbiprofen lozenge (n=212): –31.69 (95% CI: –36.72, –26.66) Change from baseline in DSS (LS mean) at 2 h - Flurbiprofen spray (n=205): –36.53 (95% CI: –42.79, –30.26) - Flurbiprofen lozenge (n=212): –36.04 (95% CI: –42.27, –29.81) AUC for DSS from 0–2 h - Flurbiprofen spray (n=205): –25.84 (95% CI: –29.47, –22.21) - Flurbiprofen lozenge (n=212): –24.86 (95% CI: –28.46, –21.25)	Single dose - In both treatment groups, DSS significantly improved at 1 and 2 h post-dose compared with baseline (p<0.0001) - There was no significant difference between spray and lozenges
	QuaSTI score (difficult to swallow)	Flurbiprofen spray (n=217): 7 (min, max: 0, 10) Flurbiprofen lozenge (n=222): 7 (min, max: 0, 10)	NR	Single dose Mean change from baseline to 2 h post-dose in the QuaSTI difficulty swallowing score showed significant improvement for both formulations (p<0.0001)
Randomized, double-blind, placebo-controlled, multiple-dose, multicenter study to determine the analgesic efficacy of flurbiprofen 8.75 mg microgranules vs placebo for patients with sore throat due to upper respiratory tract infection				
Russo, Br J Gen Pract 2013 ³⁸	DSS (mm)	Flurbiprofen microgranules (n=186): 63.1 (14.8) Placebo (n=187): 62.1 (14.9)	NR	Single dose - Significant decreases in difficulty in swallowing were observed with flurbiprofen vs placebo from 5 to 360 min after the first dose (p<0.05), and at 3 and 6 h in the AUC analysis (p=0.0011 and p=0.0003, respectively) Multiple dose - Significantly greater mean change from baseline in difficulty in swallowing with flurbiprofen vs placebo at the end of day 1 (p=0.018), day 2 (p=0.016) and day 3 (p=0.032)

Notes: ^aWhere more than one dose of flurbiprofen was studied, only data for the 8.75 mg dose are included. ^bCombined data from NCT01048866 and NCT01049334.
Abbreviations: AUC, area under the curve; DSS, Difficulty Swallowing Scale; LS, least squares; NR, full data not reported; QuaSTI, Qualities of Sore Throat Index.

Table 5 Summary of Studies Reporting Sensation of Swollen Throat Outcomes^a

References	Outcome Measure	Baseline Score Mean (SD)	Endpoint	Outcomes
Randomized, double-blind, single-dose, placebo-controlled, single-center study to assess the efficacy of flurbiprofen 8.75 mg lozenges in patients with acute sore throat (NCT01986361)				
Schachtel, Pain Manag 2018 ²⁸	QuaSTI (sensation of swollen throat)	Flurbiprofen lozenge (n=101): 7.7 (1.84) Placebo (n=21): 6.9 (2.26)	NR	Single dose Patients using flurbiprofen reported significant reductions of scores from baseline in sensation of swollen throat at 1, 2 and 3 h (all p<0.01)
Randomized, double-blind, placebo-controlled, multiple-dose, single-center, parallel-group study of the efficacy of flurbiprofen 8.75 mg lozenges compared with placebo lozenges in adult patients with acute sore throat (NCT01049334)				
Schachtel, Pain 2014 ¹⁷	SwoTS (mm)	Flurbiprofen lozenge (n=102): 76.6 (13.98) Placebo (n=102): 79.0 (12.05)	Summed difference in swollen throat over 2 h (mm*h) - Flurbiprofen (n=102): -39.9 (39.63) - Placebo (n=102): -20.1 (27.28)	Single dose - The summed difference in SwoTS over 2 h was significantly greater with flurbiprofen vs placebo (p<0.001) - By 60 min (first assessment time) there was a 25% reduction in the sensation of a swollen throat with flurbiprofen vs 13% with placebo (p<0.001) - At 2 h, patients treated with flurbiprofen reported a 26% reduction in SwoTS vs 12% with placebo (p<0.001) - Flurbiprofen-treated patients reported a 39% peak reduction of swollen throat vs 25% for placebo (p<0.001) - Flurbiprofen was associated with significantly greater absolute (and percentage) reduction in SwoTS compared with placebo (p<0.05) for up to 210 min
Aspley, Curr Med Res Opin 2016 ²⁹	SwoTS (mm)	Flurbiprofen lozenge (n=59): 80.3 (11.5) Placebo (n=65): 80.8 (11.38)	Time-weighted summed reduction in SwoTS score (LS mean) over 24 h (mm*h) - Flurbiprofen (n=58): 501.7 - Placebo (n=65): 296.4	Single dose - Flurbiprofen provided significantly greater reduction in all patients with swollen throat vs placebo from 60 min (first assessment) through to 180 min (p<0.05) Multiple dose 69.3% greater reduction in sensation of swollen throat with flurbiprofen vs placebo (difference of 205.3 mm*h; 95% CI: 41.0, 369.6; p<0.05) over 24 h - For patients who had relatively severe sensation of swollen throat, flurbiprofen provided 148.6% greater relief of swollen throat than placebo (difference of 361.6 mm*h; 95% CI: 169.9, 553.3; p<0.001) over 24 h

Schachtel, Pain Manag 2016 ³⁶	SwoTS (mm)	Flurbiprofen lozenge (n=102): 76.6 (13.98) Placebo (n=102): 79.0 (12.05)	Summed difference in SwoTS scores (LS mean) over 24 h (mm ^{3h}) • Flurbiprofen (n=101): -482.4 • Placebo (n=99): -344.8 Difference in DSS score from pre-dose to 2 h post-dose (LS means) over 2-7 days (mm) • Flurbiprofen (n=94): -15.0 • Placebo (n=96): -9.2	Multiple dose • 40% greater improvement in swallowing with flurbiprofen vs placebo (difference of -137.6 mm^{3h}; 95% CI: -268.5, -68; p=0.04) over 24 h • Subsequent uses of flurbiprofen (over 2-7 days) provided 63% greater improvement in swallowing vs placebo (difference of -5.7 mm; 95% CI: -9.5, -1.9; p<0.01)
Shepherd, Int J Clin Pract 2015 ^{37,b}	SwoTS (mm)	Flurbiprofen lozenge (n=203): 76.3 (13.4) Placebo (n=199): 77.6 (12.5)	NR	Single dose • Flurbiprofen provided significantly greater reduction in sensation of swollen throat vs placebo for the entire population for up to 4 h (p<0.01) Multiple dose • Flurbiprofen over 24 h provided 40.5% greater relief of swollen throat vs placebo in the entire population (p<0.0001)
Randomized, double-blind, placebo-controlled, parallel-group study to examine the efficacy and safety of multiple doses of flurbiprofen 8.75 mg lozenge, with a focus on the initial 24 h of treatment (NCT01048866)				
Schachtel, Trials 2014 ³⁰	SwoTS (mm)	Flurbiprofen lozenge (n=101): 76.0 (12.9) Placebo (n=97): 76.0 (12.8)	Summed difference in SwoTS scores (LS mean) over 24 h (mm ^{3h}) • Flurbiprofen (n=99): -550.8 • Placebo (n=95): -382.4	Single dose • Reductions in absolute SwoTS scores were observed at each hourly assessment up to and including 4 h post-dose with flurbiprofen vs placebo (p<0.05) • Significantly more patients reported ≥20% reduction in swollen throat with flurbiprofen vs placebo (63.4% and 40.2%, respectively; p<0.01) Multiple dose • 44% greater relief of sensation of swollen throat with flurbiprofen vs placebo (difference of -168.4 mm^{3h}; 95% CI: -293.7, -43.1; p<0.01) over 24 h • Patients taking flurbiprofen over days 2-7 experienced a 45% greater relief of swollen throat (difference of -8.1 mm; 95% CI: -16.8, 0.6; p=0.07) vs placebo
Randomized, double-blind, parallel-group, single-center study comparing the efficacy and tolerability of flurbiprofen lozenges (8.75 mg or 12.5 mg) with placebo in the treatment of patients with sore throat due to upper respiratory tract infection				

(Continued)

Table 5 (Continued).

References	Outcome Measure	Baseline Score Mean (SD)	Endpoint	Outcomes
Benrimoj, Clin Drug Investig 2001 ³²	SwoTS (mm)	Flurbiprofen lozenge (n=128): 70.0 (11.8) Placebo (n=128): 69.7 (11.2)	Sum of changes from baseline in sensation of swollen throat over 15–120 min - Flurbiprofen (n=120): -124.4 (9.6) - Placebo (n=125): -92.9 (9.2) Sum of changes from baseline in sensation of swollen throat over 15–360 min - Flurbiprofen (n=118): -183.7 (15.5) - Placebo (n=122): -142.3 (14.2)	Single dose - Flurbiprofen was associated with significantly greater reduction of sensation of swollen throat from baseline over 15–120 min ($p=0.015$) and over 15–360 min ($p=0.042$) vs placebo - Significantly greater reductions in swollen throat were seen at 30 min, and at each assessment point up to 4 h, with flurbiprofen vs placebo ($p<0.05$)
Randomized, double-blind, parallel-group, placebo-controlled, single- and multiple-dose, single-center study to assess the efficacy and safety of flurbiprofen 8.75 mg and 12.5 mg lozenges in patients with relatively severe sore throat due to upper respiratory tract infection				
Watson, Int J Clin Pract 2000 ²²	SwoTS (mm)	Flurbiprofen lozenge (n=129): 61.43 (13.14) Placebo (n=129): 60.66 (16.36)	Sum of change from baseline in sensation of swollen throat over 15–120 min - Flurbiprofen (n=127): -70.46 (7.1) - Placebo (n=128): -63.93 (7.4) Sum of change from baseline in sensation of swollen throat over 15–360 min - Flurbiprofen (n=116): -119.79 (11.5) - Placebo (n=117): -110.52 (13.1)	Single dose - There were no significant differences between flurbiprofen and placebo for swollen throat over 2 and 6 h ($p=0.544$ and $p=0.615$, respectively) Multiple dose - Swollen throat was significantly reduced with flurbiprofen vs placebo on days 3 ($p=0.005$) and 4 ($p=0.001$)
Randomized, double-blind, placebo-controlled, parallel-group study to assess the efficacy of flurbiprofen 8.75 mg spray in adults with sore throat due to upper respiratory tract infection (ACTRN12612000457842)				

de Looze, Eur J Gen Pract 2016 ³⁴	SwoTS (mm)	Flurbiprofen spray (n=249): 66.53 (13.63) Placebo (n=256): 67.62 (11.79)	NR	Single dose - Significantly greater change from baseline in SwoTS with flurbiprofen at 2, 3 and 6 h compared with placebo ($p<0.0001$) Multiple dose - Compared with placebo, flurbiprofen spray provided a greater reduction in the change from baseline in swollen throat at the end of day 1, at 24 h (± 15 min), and at the end of days 2 and 3 ($p<0.05$ for all, except the end of day 3; $p<0.147$)
Multicenter, double-blind, double-dummy, non-inferiority study to assess the efficacy of flurbiprofen 8.75 mg delivered as a spray or lozenge in patients with sore throat due to upper respiratory tract infection				
Burova, J Pain Res 2018 ²⁵	SwoTS (mm)	Flurbiprofen spray (n=217): 59.7 (17.08) Flurbiprofen lozenge (n=222): 60.6 (15.49)	Change from baseline in SwoTS (LS mean) at 1 h - Flurbiprofen spray (n=205): -26.64 (95% CI: -32.24, -21.03) - Flurbiprofen lozenge (n=212): -25.57 (95% CI: -31.14, -20.00) Change from baseline in DSS (LS mean) at 2 h - Flurbiprofen spray (n=205): -30.51 (95% CI: -36.21, -24.81) - Flurbiprofen lozenge (n=212): -29.48 (95% CI: -35.14, -23.82) AUC for SwoTS (LS means) from 0–2 h - Flurbiprofen spray (n=205): -20.98 (95% CI: -24.78, -17.18) - Flurbiprofen lozenge (n=212): -20.13 (95% CI: -23.9, -16.35)	Single dose - Scores for swollen throat significantly ($p<0.0001$) improved at 1 and 2 h post-dose compared with baseline with both formulations - There was no significant difference between formulations in change in swollen throat
	QuaSTI (sensation of swollen throat)	Flurbiprofen spray (n=217): 6 (min, max: 0, 10) Flurbiprofen lozenge (n=222): 6 (min, max: 0, 10)	NR	Single dose Mean change from baseline to 2 h post-dose in the QuaSTI swollen throat score showed significant improvement for both formulations ($p<0.0001$)

Notes: ^aWhere more than one dose of flurbiprofen was studied, only data for the 8.75 mg dose are included. ^bCombined data from NCT01048866 and NCT01049334.

Abbreviations: AUC, area under the curve; DSS, Difficulty Swallowing Scale; LS, least squares; NR, not reported; QuaSTI, Qualities of Sore Throat Index; SwoTS, Swollen Throat Scale.

Only one study reported no difference between single-dose flurbiprofen and placebo in reduction of sensation of swollen throat over 2 and 6 h, but did report significant reductions in the symptom on days 3 ($p=0.005$) and 4 ($p=0.001$) of multiple dosing.²²

Onset of Action

Several studies indicated that locally administered flurbiprofen can provide symptomatic relief from sore throat and associated symptoms from 1–30 min after taking a single dose, depending on the first assessment time point (Table 6).^{17,22,25,29,32–35,38} Burova et al²⁵ reported that at least 90% of patients using single-dose flurbiprofen 8.75 mg spray or lozenge experienced at least “slight” sore throat relief (on the STRRS) from 1 min post completion of dose, with 55–59% of patients reporting “at least moderate relief” – an established measure of clinically meaningful effect – from 1 min. Similarly, Russo et al³⁸ reported a significantly greater reduction in mean throat soreness with flurbiprofen 8.75 mg microgranules ($p<0.001$) and a significantly greater improvement in sore throat relief ($p<0.0006$) compared with placebo at 1 min post-dose.

Studies have also demonstrated early onset of relief from difficulty swallowing and sensation of swollen throat.^{29,32,34,38} A significantly greater reduction in difficulty swallowing with flurbiprofen compared with placebo was reported at 5 min post-dose by de Looze et al³⁴ and Russo et al³⁸ in patients using spray or microgranule formulations of flurbiprofen, and at 10 min post-dose (the first assessment time point) with lozenges (all $p<0.05$).²⁹ A significantly greater reduction in sensation of swollen throat was also achieved at 30 min post-dose vs placebo with lozenges ($p<0.05$)³² and with flurbiprofen spray ($p<0.001$).³⁴

Onset of analgesia attributable to the active ingredient of a lozenge is complicated by the inherent demulcent effect of the sugary vehicle base of the lozenge itself, which provides an immediate, but short-lived, soothing effect as a result of increasing salivation and lubrication of the mucosa.^{24,44} Assessments at 2-min intervals during the early stages of studies have demonstrated this effect.^{17,29} Several of the reviewed studies specifically assessed the onset of clinically relevant, or “meaningful”, analgesia with flurbiprofen in order to distinguish the analgesic effect of flurbiprofen from the demulcent effect of the lozenge base.^{17,33,35,38} As mentioned previously in the “Meaningful Pain Relief” section, median onset of pharmacological activity (“time to the

first perceived reduction of sore throat pain” confirmed by “at least moderate pain relief”) was 12 min in patients taking flurbiprofen lozenge, compared with over 120 min (last assessment time) for the placebo group ($p<0.001$) in the study by Schachtel et al.¹⁷ In another paper from Schachtel et al,³⁵ using the previously described DSW method, median time to “first perceived pain relief” for flurbiprofen-treated patients was 11 min (95% CI: 7.6, 14.3 min) compared with 19 min (95% CI: 4.8, 30.3 min) for placebo-treated patients ($p=0.03$). However, median time to “meaningful pain relief” was 43 min (95% CI: 36.4, 49.4 min) with flurbiprofen, (significantly different from placebo-treated patients; $p=0.01$). A subgroup analysis in patients with more severe sore throat reported a median time to “meaningful” relief of 47 min (95% CI: 35.4, 78.1 min) and a median time to “first perceived” relief of 16 min (95% CI: 7.3, 25.2 min) with flurbiprofen, both of which were significantly different from placebo ($p=0.01$ and $p=0.04$, respectively).

In the paper by Russo et al,³⁸ in which onset of sore throat relief was evident at 1 min post-dose, the degree of change in throat soreness classified as “clinically important” (a reduction of 1–2 points on the 11-point ordinal TSS) was achieved with flurbiprofen microgranules at 30 min post-dose. de Looze et al³³ reported significantly greater sore throat relief with flurbiprofen spray from 20 min (first assessment time point) post-dose ($p<0.0001$), with “meaningful” relief (sore throat severity reduced by at least 2.2 mm on the TSS) achieved at 75 min post-dose.

Duration of Action

Data from several studies suggest that single-dose flurbiprofen can provide long-lasting symptomatic relief of sore throat and associated symptoms over several hours (Table 6).^{17,22,25,29,30,32–34,37,38} de Looze et al³⁴ reported significantly greater reductions in throat soreness ($p<0.01$), pain intensity ($p<0.01$), difficulty swallowing ($p<0.05$) and sensation of swollen throat ($p<0.001$), and significantly greater improvements in sore throat relief ($p<0.001$) with flurbiprofen spray vs placebo for up to 6 h post-dose. Similarly, Russo et al³⁸ demonstrated significantly greater (and clinically relevant) improvements in sore throat relief and significantly greater reductions in difficulty swallowing ($p<0.05$ for both) with flurbiprofen microgranules vs placebo for up to 6 h post-dose (the last assessment time point). Studies investigating flurbiprofen lozenges have reported significantly greater reductions in throat soreness, pain intensity, difficulty swallowing and sensation of

Table 6 Summary of Studies Reporting Onset and Duration of Action of Single-dose Flurbiprofen^a

References	Assessment Schedule	First and Last Assessment Time Points	Onset of Action with Flurbiprofen	Duration of Action of Flurbiprofen
Lozenges				
Randomized, double-blind, single-dose, placebo-controlled, single-center study to assess the efficacy of flurbiprofen 8.75 mg lozenges in patients with acute sore throat (NCT01986361)				
Schachtel, Br J Pain 2018 ³⁵	STTS: every 5 min during the first hour and every 10 min during the second and third hours STPIS: 1, 2, and 3 h and at the time the second stopwatch was stopped (indicating "meaningful relief")	5 min to 3 h	- Median time to "first perceived relief": 11 min (95% CI: 7.6–14.3 min) - Median time to "first perceived relief" confirmed by "meaningful relief": 13 min (95% CI: 8.6–16.6 min) - Median time to "meaningful relief": 43 min (95% CI: 36.4–49.4 min)	Greater achievement of "meaningful relief" vs placebo for at least 3 h ($p<0.01$)
Schachtel, Pain 2014 ¹⁷	STPIS: every 2 min during the first hour; every 10 min during the second hour; every 30 min from 2–6 h	2 min to 6 h	- Onset of first reduction of sore throat pain: 2 min - Median time to first perceived reduction of sore throat pain confirmed by at least moderate pain relief: 12 min - First significant absolute reduction in sore throat pain vs placebo: 22 min ($p<0.05$) - First significant percentage reduction in sore throat pain vs placebo (indicative of change relative to each patient's pretreatment pain intensity): 26 min ($p<0.05$)	Greater absolute reduction in pain vs placebo up to 4 h ($p<0.05$)
	STRRS: every 10 min during the second hour; every 30 min from 2–6 h	1 h to 6 h	Significant difference in sore throat relief from first assessment at 1 h vs placebo ($p<0.05$)	Significant differences in sore throat relief vs placebo: up to 4 h ($p<0.05$)
Randomized, double-blind, placebo-controlled, multiple-dose, single-center, parallel-group study of the efficacy of flurbiprofen 8.75 mg lozenges compared with placebo lozenges in adult patients with acute sore throat (NCT01049334)				
Aspley, Curr Med Res Opin 2016 ²⁹	STPIS: every 2 min during the first hour; every 10 min during the second hour; every 30 min from 2–6 h; hourly from 6–24 h	2 min to 6 h	First significant reduction in sore throat pain vs placebo: 22 min ($p<0.05$)	Significant reduction in sore throat pain vs placebo: up to 210 min ($p<0.05$)
	DSS: every 10 min during first 2 h; every 30 min from 2–6 h; hourly from 6–24 h	10 min to 6 h	Significant reduction in difficulty swallowing vs placebo at first assessment at 10 min ($p<0.05$)	Significant reduction in difficulty swallowing vs placebo: up to 210 min ($p<0.05$)
	SwoTS: at 1 h, then every 10 min during second hour; every 30 min from 2–6 h; hourly from 6–24 h	1 h to 24 h	Significant reduction in sensation of swollen throat vs placebo from first assessment at 1 h ($p<0.05$)	Significant reduction in sensation of swollen throat vs placebo: up to 3 h ($p<0.05$)
Randomized, double-blind, placebo-controlled, parallel-group study to examine the efficacy and safety of multiple doses of flurbiprofen 8.75 mg lozenge, with a focus on the initial 24 h of treatment (NCT01048866)				

(Continued)

Table 6 (Continued).

References	Assessment Schedule	First and Last Assessment Time Points	Onset of Action with Flurbiprofen	Duration of Action of Flurbiprofen
Schachtel, Trials 2014 ³⁰	STPIS: hourly for 24 h	1 h to 6 h	Significant reduction in sore throat pain from first assessment at 1 h vs placebo ($p<0.01$)	Significant reduction in sore throat pain vs placebo: up to 3 h ($p<0.01$)
	DSS: hourly for 24 h	1 h to 6 h	Significant reduction in difficulty swallowing from first assessment at 1 h vs placebo ($p<0.001$)	Significant reduction in difficulty swallowing vs placebo: up to 4 h ($p<0.05$)
	SwoTS: hourly for 24 h	1 h to 6 h	Significant reduction in sensation of swollen throat from first assessment at 1 h vs placebo ($p<0.001$)	Significant reduction in sensation of swollen throat vs placebo: up to 4 h ($p<0.05$)
Shepherd, Int J Clin Pract 2015 ^{37b}	STPIS: hourly for 24 h	1 h to 6 h	Significant reduction in throat pain from first assessment at 1 h vs placebo ($p<0.0001$)	Significant reduction in throat pain vs placebo: up to 4 h ($p<0.01$)
	DSS: hourly for 24 h	1 h to 6 h	Significant improvement in difficulty swallowing from first assessment at 1 h vs placebo ($p<0.0001$)	Significant reduction in difficulty swallowing vs placebo: up to 4 h ($p<0.01$)
	SwoTS: hourly for 24 h	1 h to 6 h	Significant improvement in sensation of swollen throat from first assessment at 1 h vs placebo ($p<0.0001$)	Significant reduction in sensation of swollen throat vs placebo: up to 4 h ($p<0.01$)
Randomized, double-blind, parallel-group, single-center study comparing the efficacy and tolerability of flurbiprofen lozenges (8.75 mg or 12.5 mg) with placebo in the treatment of patients with sore throat due to upper respiratory tract infection				
Benrimoj, Clin Drug Investig 2001 ³²	TSS: every 15 min during the first 2 h; every hour from 2–6 h	15 min to 6 h	Significant reduction in throat soreness at 30 min vs placebo ($p<0.05$)	Significant reduction in throat soreness vs placebo: up to 4 h ($p<0.05$)
	SwoTS: every 15 min for 2 h; every hour from 2–6 h	15 min to 6 h	Significant reduction in sensation of swollen throat at 30 min vs placebo ($p<0.05$)	Significant reduction in sensation of swollen throat vs placebo: up to 3 h ($p<0.05$)
	STRRS: every 15 min for 2 h; every hour from 2–6 h	15 min to 6 h	Significant improvement in total pain relief at 45 min vs placebo ($p<0.05$)	Significant improvement in pain relief vs placebo: at least 2 h ($p<0.05$)
Randomized, double-blind, parallel-group, placebo-controlled, single- and multiple-dose, single-center study to assess the efficacy and safety of flurbiprofen 8.75 mg and 12.5 mg lozenges in patients with relatively severe sore throat due to upper respiratory tract infection				
Watson, Int J Clin Pract 2000 ²²	TSS: every 15 min for 2 h; every hour from 2–6 h	15 min to 6 h	Significant reduction in throat soreness at 15 min vs placebo ($p<0.05$)	Significant reduction in throat soreness vs placebo: at least 2 h ($p<0.05$)
Spray				

Randomized, double-blind, placebo-controlled, parallel-group study to assess the efficacy of flurbiprofen 8.75 mg spray in adults with sore throat due to upper respiratory tract infection (ACTRN1261200457842)					
de Looze, Eur J Gen Pract 2016 ³⁴	TSS: every 5 min up to 20 min; 30 min; every 15 min from 30 min to 2 h; every 30 min from 2–3 h; hourly from 3–6 h	5 min to 6 h	• Significant reduction in throat soreness from first assessment at 5 min vs placebo (p<0.01)	• Significant reduction in throat soreness vs placebo: at least 6 h (p<0.01)	
	DSS: every 5 min up to 20 min; 30 min; every 15 min from 30 min to 2 h; every 30 min from 2–3 h; hourly from 3–6 h	5 min to 6 h	• Significant reduction in difficulty swallowing from first assessment at 5 min vs placebo (p<0.05)	• Significant reduction in difficulty swallowing vs placebo: at least 6 h (p<0.05)	
	STPIS: 20 min; 30 min; every 15 min from 30 min to 2 h; every 30 min from 2–3 h; hourly from 3–6 h	20 min to 6 h	• Significant reduction in pain intensity from first assessment at 20 min vs placebo (p<0.01)	• Significant reduction in pain intensity vs placebo: at least 6 h (p<0.01)	
	SwoTS: every 15 min from 30 min to 2 h; every 30 min from 2–3 h; hourly from 3–6 h	30 min to 6 h	• Significant reduction in sensation of swollen throat from first assessment at 30 min vs placebo (p<0.001)	• Significant reduction in sensation of swollen throat vs placebo: at least 6 h (p<0.001)	
	STRRS: 20 min; 30 min; every 15 min from 30 min to 2 h; every 30 min from 2–3 h; hourly from 3–6 h	20 min to 6 h	• Significant relief from sore throat from first assessment at 20 min vs placebo (p<0.0001)	• Significant relief from sore throat vs placebo: at least 6 h (p<0.0001)	
de Looze, Pain Manag 2018 ³³	STRRS: 20 min; 30 min; every 15 min from 30 min to 2 h; every 30 min from 2–3 h; hourly from 3–6 h	20 min to 6 h	• Significant relief from sore throat from first assessment at 20 min vs placebo (p<0.0001) • Onset of “meaningful relief”: 75 min	• Significant “meaningful” sore throat relief vs placebo: at least 6 h (p<0.0001)	
Multicenter, double-blind, double-dummy, non-inferiority study to assess the efficacy of flurbiprofen 8.75 mg delivered as a spray or lozenge in patients with sore throat due to upper respiratory tract infection					
Burova, J Pain Res 2018 ²⁵	STRRS: 1 min; 1 and 2 h	1 min to 2 h	• At 1 min post-dose, 90% of patients experienced at least “slight” pain relief (≥1 on the STRRS) with flurbiprofen spray and 93% with the lozenge • At 1 min post-dose, 55% of patients reported clinically meaningful pain relief with flurbiprofen spray and 59% with the lozenge	• Significant “meaningful” sore throat relief for both spray and lozenge: at least 2 h (p>0.05) • No significant difference between spray and lozenge	
	DSS: 1 and 2 h	1 h to 2 h	• Significant improvement from baseline in difficulty swallowing from first assessment at 1 h (p<0.0001)	• Significant reduction of difficulty swallowing from baseline for both spray and lozenge: at least 2 h (p>0.05) • No significant difference between spray and lozenge	
	SwoTS: 1 and 2 h	1 h to 2 h	• Significant improvement from baseline in sensation of swollen throat from first assessment at 1 h (p<0.0001)	• Significant reduction of difficulty swallowing from baseline for both spray and lozenge: at least 2 h (p>0.05) • No significant difference between spray and lozenge	
Microgranules					

(Continued)

Table 6 (Continued).

References	Assessment Schedule	First and Last Assessment Time Points	Onset of Action with Flurbiprofen	Duration of Action of Flurbiprofen
Randomized, double-blind, placebo-controlled, multiple-dose, multicenter study to determine the analgesic efficacy of flurbiprofen 8.75 mg microgranules vs placebo for patients with sore throat due to upper respiratory tract infection				
Russo, Br J Gen Pract 2013 ³⁸	TSS: 1 min; every 5 min up to 15 min; every 15 min from 15 min to 3 h; every hour from 3–6 h	1 min to 6 h	• Significant reduction in throat soreness from first assessment at 1 min vs placebo (p<0.001)	• Significant reduction in throat soreness vs placebo: up to 300 min (p<0.05)
	STRRS: 1 min; every 5 min up to 15 min; every 15 min from 15 min to 3 h; every hour from 3–6 h	1 min to 6 h	• Significant improvement in sore throat relief from first assessment at 1 min vs placebo (p=0.0006)	• Significant improvement in sore throat relief vs placebo: at least 6 h (p<0.05)
	STPIS: 1 min; every 5 min up to 15 min; every 15 min from 15 min to 3 h; every hour from 3–6 hrs	1 min to 6 h	• Significant reduction in pain intensity at 5 min vs placebo (p<0.05)	• Significant reduction in pain intensity vs placebo: at least 6 h (p<0.05)
	DSS: 1 min; every 5 min up to 15 min; every 15 min from 15 min to 3 h; every hour from 3–6 h	1 min to 6 h	• Significant reduction in difficulty swallowing from 5 min vs placebo (p<0.05)	• Significant reduction in difficulty swallowing vs placebo: at least 6 h (p<0.05)

Notes: ^aWhere more than one dose of flurbiprofen was studied, only data for the 8.75 mg dose are included. ^bCombined data from NCT01048866 and NCT01049334. Abbreviations: DSS, Difficulty Swallowing Scale; STS, Sore Throat Scale; STPIS, Sore Throat Pain Intensity Scale; STRRS, Sore Throat Relief Rating Scale; TSS, Throat Soreness Scale; SwoTS, Swollen throat Scale.

swollen throat, and significantly improved sore throat relief vs placebo for at least 2–4 h, dependent on the study assessment period.^{17,22,29,30,32,35,37}

Other Symptoms Associated with Sore Throat Qualities of Sore Throat Index (QuaSTI)

Patients with pharyngitis commonly report a number of symptoms beyond just “sore throat” when they seek professional intervention, and these symptoms may be described using a wide variety of sensory, emotional, and functional terms.²⁸ Two papers^{25,28} have assessed the ability of flurbiprofen to provide relief from 10 features of sore throat commonly reported by patients using the recently developed and validated QuaSTI (Table 2).

Schachtel et al²⁸ demonstrated a significant improvement (ie reduction in mean overall QuaSTI score) from baseline to 3 h post-dose with single-dose flurbiprofen lozenge (mean ±SD, −19.3 ± 18.62; p<0.001). This improvement was significantly greater with flurbiprofen compared with placebo lozenge (154%; p<0.05). With regards to the individual qualities of sore throat, patients using flurbiprofen lozenge consistently reported significant reductions of scores from baseline at 1, 2, and 3 h (all p<0.01). In addition, the changes in QuaSTI were confirmed as “clinically significant” for some of the individual qualities, with differences from pretreatment levels of at least two points on the Likert scales for swollen throat, difficulty swallowing, agonizing and throat soreness.

Burova et al²⁵ demonstrated a significant improvement from baseline to 2 h post-dose for the sum score of all items on the QuaSTI for both flurbiprofen spray (mean ±SD, −29.0 ± 16.07; 95%CI: −31.20, −26.90) and lozenge (−27.9 ± 16.31; 95%CI: −30.10, −25.80) (p<0.0001 from baseline for both). There was a reduction from baseline to 2 h of at least two points for all the individual symptoms of sore throat on the QuaSTI, signifying “clinically significant” changes.

URTI Symptoms

Sore throat associated with acute URTI is often accompanied by other troublesome upper respiratory tract symptoms, for example cough, post-nasal drip, swollen or tender neck glands, tickly throat, achiness and lack of energy.^{25,28} These can be assessed using the URTI questionnaire (Table 2). Schachtel et al²⁸ observed that significant numbers of patients treated with flurbiprofen lozenges, but not placebo, reported an absence of several URTI symptoms (achiness, pressure around the eyes, mouth breathing, lack of energy, tender neck glands,

headache, loss of appetite, sinus pressure, coughing, chest tightness, or sinus pain) at 3 h post-dose compared to pretreatment (all $p < 0.05$). In particular, among patients reporting cough at baseline, 46% (11/24 patients) reported no coughing at 3 h ($p = 0.01$).

Burova et al²⁵ also demonstrated a significant reduction in the number of patients experiencing URTI symptoms with both flurbiprofen spray and lozenges. At 2 h post-dose, the number of patients experiencing URTI symptoms that can be attributed to or associated with sore throat (coughing, post-nasal drip, swollen neck glands, tender neck glands, throat tickle, and throat clearing) decreased relative to baseline. These decreases were statistically significant for every symptom, except tender neck glands (lozenge only; $p = 0.0881$) and throat tickle (both formulations; $p = 0.3113$ for spray and $p = 0.2249$ for lozenge). There was an 85% and 54% reduction in the number of patients with cough from baseline to 2 h with spray and lozenge, respectively.

Streptococcal versus Non-Streptococcal Pharyngitis

The effectiveness of flurbiprofen in patients with or without strep A/C sore throat has been assessed in several of the reviewed papers.^{26,28,35,37} In a paper by Shephard et al,³⁷ subgroup data from two clinical trials were combined to evaluate the efficacy of flurbiprofen lozenges in patients with and without microbiologically proven strep A/C. Strep A/C was confirmed in 24% (96/401) of patients who had a throat culture test. Significant pain reduction (on the STPIS) with single-dose flurbiprofen compared with placebo was observed for up to 4 h ($p < 0.01$) for the overall population and for patients without strep A/C, and for up to 3 h for patients with strep A/C (both $p < 0.05$). There were no differences in treatment effects in the strep A/C group compared with the non-strep A/C group ($p > 0.2$ for all time points assessed up to 6 h). Likewise, there were no significant differences in flurbiprofen single-dose treatment effects in the strep A/C group compared with the non-strep A/C group for either difficulty swallowing or swollen throat ($p > 0.05$ for all time points assessed up to 6 h). With multiple-dose flurbiprofen, reductions in pain intensity, and improvements in difficulty swallowing and swollen throat, were also similar regardless of strep A/C status, although the improvements observed in the strep A/C group were not statistically different from placebo, possibly due to the small patient numbers or the natural improvement of throat symptoms over time.

In a study by Schachtel et al, strep A/C was detected in 34% (42/122) of patients, and efficacy of flurbiprofen lozenges in reducing sore throat symptoms (on the QuaSTI) was similar regardless of strep A/C status.²⁸ In a further analysis of the data,³⁵ among flurbiprofen-treated patients with strep A/C, 82% reported “meaningful” pain relief (on the STPIS) within 3 h compared with 78% in the non-strep group. Moreover, there was no significant difference in median time to “meaningful” relief for flurbiprofen-treated patients with or without strep A/C (41 min vs 43 min, respectively; $p = 0.39$). All patients with strep A/C reported “first perceived pain relief” with flurbiprofen within the 3-h study period. Likewise, in a study from Radkova et al,²⁶ although only 5.4% (22/411) of patients tested positive for strep A/C sore throat, subgroup analyses showed similar efficacy (change in pain intensity on the STPIS at 2 h) with flurbiprofen spray and lozenges regardless of strep A/C status.

Concomitant Antibiotic Use

In a study from Blagden et al,³¹ 59% (135/230) of flurbiprofen lozenge-treated patients also took concomitant antibiotics, as did 58% (133/229) of placebo-treated patients. Antibiotic usage did not affect sore throat relief (reported as TOTPAR) over days 1–4 within the flurbiprofen treatment group.

Patient Satisfaction/Overall Treatment Rating

In addition to assessing the efficacy of flurbiprofen in managing the symptoms of sore throat, several of the studies also evaluated patients’ opinions of the overall success of the treatment, most using the Global Evaluation Scale (GLOBAL), the Satisfaction Scale (SATIS) and/or an overall treatment rating scale (Table 2).^{22,25,26,30–32,34,36,38}

Significantly more patients taking flurbiprofen rated their treatment as “good”, “very good” or “excellent” on the GLOBAL compared with placebo after single- and multiple-dose treatment.^{34,36} Similarly, there was greater patient satisfaction on the SATIS after treatment, with a significantly higher proportion of patients reporting that they were “satisfied”, “very satisfied” or “extremely satisfied” with flurbiprofen compared with placebo.^{30,36} There were no significant differences between flurbiprofen spray and lozenges in terms of GLOBAL²⁵ or SATIS.²⁶ Flurbiprofen was also associated with benefit over placebo in studies using an overall treatment rating scale,^{22,31,32} and in a paper from Russo et al³⁸ patients reported feeling

significantly less distracted, less frustrated, and happier after taking flurbiprofen microgranules for 3 days compared with placebo ($p < 0.05$).

Post-Operative Sore Throat (POST)

Two clinical studies investigating the effectiveness of flurbiprofen for the prevention of POST were eligible for inclusion in the review (Table 1).^{40,41} Uztüre et al⁴¹ evaluated the efficacy of flurbiprofen lozenges for preventing POST, hoarseness and dysphagia symptoms in patients in whom a ProSeal laryngeal mask airway (LMA) was inserted during general anesthesia. A single flurbiprofen lozenge, given 45 min before induction of anesthesia, effectively reduced the severity of early POST (30 min postoperatively) and dysphagia compared with placebo ($p < 0.05$ for both). Likewise, dysphagia was significantly lower in the flurbiprofen group compared with placebo at 4 h and hoarseness at 12 h postoperatively ($p < 0.05$ for both). The incidence of POST symptoms was not significantly different between the flurbiprofen and placebo groups throughout the duration of the study.

In the second study, Aydin et al⁴⁰ compared flurbiprofen lozenges with a sea salt and glycerine spray, a gargle used for the prevention of symptoms associated with stomatitis and gingivitis, and no treatment (control group) for the prevention of POST in 320 patients ($n = 80$ for each treatment group) undergoing elective genitourinary surgery under general anesthesia. Treatment was again given 45 min prior to induction of anesthesia. There was a significantly lower incidence of POST in the flurbiprofen lozenge and Siccoral[®] (Assos Pharmaceuticals, Istanbul, Turkey) spray groups at 0 and 1 h compared with those not treated ($p < 0.01$ for all). There was a significantly lower incidence of POST in the Siccoral[®] spray group compared with the flurbiprofen group at 0 h post-extubation ($p = 0.002$), but the incidence of POST was similar between all groups at 6 and 24 h post-extubation ($p = 0.141$ and $p = 0.426$, respectively).

Although not eligible for full inclusion in this review due to the use of a lower dose of flurbiprofen (0.325 mg per spray; two sprays to each tonsillar fossa) the efficacy of flurbiprofen spray (three times a day for 7 days), has also been demonstrated for the management of post-tonsillectomy pain.⁴³ The severity of throat pain was lower in the flurbiprofen group ($n = 45$) when compared with the placebo group ($n = 39$), and this difference was statistically significant for all assessment days. Moreover, the flurbiprofen group required significantly less rescue analgesic

than the placebo group during the study period on days 1, 3, 5, and 7.

Safety

Safety data from the reviewed studies are summarized in Table 7. Overall, flurbiprofen 8.75 mg was well tolerated, regardless of formulation; in the majority of studies the incidence of treatment-emergent adverse events (TEAEs) was similar between the flurbiprofen and placebo treatment groups.^{17,28–30,33–38} The incidence of AEs was also similar between flurbiprofen and placebo in patients who were positive for strep A/C.³⁷ In three papers the incidence of TEAEs was significantly higher with flurbiprofen vs placebo,^{22,31,32} taste perversion was the most commonly reported TEAE in these studies. Reports of taste perversion varied in their description by the patient; peppery taste, transient stinging or burning sensation, and unpleasant, bad or sour taste.^{22,31,32} No relationship between taste perversion and changes to the oral mucosa was demonstrated on oral examination,^{22,31,32} with the effect lasting only until dissolution of the lozenge was complete.²² When taste perversion was removed from the analyses there was no significant difference in incidence of AEs between treatment groups.^{22,32}

Most AEs thought to be “definitely”, “probably” or “possibly” related to treatment were mild and transient, with no serious AEs reported for any of the formulations of flurbiprofen 8.75 mg. In addition to taste perversion, treatment-related AEs were most commonly associated with the digestive system (nausea, dyspepsia, diarrhea, abdominal pain/discomfort) or the nervous system (dry mouth, paresthesia, throat irritation). Discontinuations due to AEs were rare and generally resulted from AEs subsequently not considered to be of clinical relevance³¹ or thought to be related to underlying medical conditions.³⁶ Radkova et al²⁶ observed no significant differences in the incidence of TEAEs between the lozenge and the spray formulations.

Summary

Low dose (8.75 mg), locally administered flurbiprofen has been shown in the reviewed studies to provide effective relief of acute sore throat, including relief of throat pain and soreness, difficulty swallowing, sensation of swollen throat, and many other commonly reported qualities of sore throat.^{17,22,25,26,28–38} This efficacy has been demonstrated across all the different locally administered formulations studied (lozenge, spray or microgranules),

Table 7 Summary of Flurbiprofen Adverse Events^a

Reference	Reporting Period	Patients Reporting TEAEs % (n/N)		Patients Reporting Drug-related AEs % (n/N)		Patients Reporting Severe AEs ^b % (n/N)		Discontinuations Due to AEs % (n/N)		Key AEs
		Flurb	Placebo	Flurb	Placebo	Flurb	Placebo	Flurb	Placebo	
Schachtel 2018 ^{28,35}	3 h	9.9 (10/101) ^c	4.8 (1/21)	3.0 (3/101)	0 (0/101)	1.0 (1/101)	0	0	0	Abdominal discomfort Throat irritation Nausea Pyrexia
Schachtel 2014 ¹⁷	6 h	14.7 (15/102) ^c	18.6 (19/102)	NR	NR	0	0	0	0	Nausea Headache
Aspley 2016 ²⁹	24 h	25.4 (15/59) ^c	27.7 (18/65)	NR	NR	0	0	0	0	Nausea Headache Abdominal pain
Schachtel 2016 ³⁶	7 days	35.3 (36/102) ^c	32.4 (33/102)	19.6 (20/102) ^d	7.8 (8/102)	3.9 (4/102) ^c	3.9 (4/102)	2.0 (2/102)	3.0 (3/102)	Stomatitis/oral pain Oral paresthesia Abdominal pain Nausea
Shephard 2015 ³⁷	24 h	24.1 (49/203) ^c	22.1 (44/199)	NR	NR	NR	NR	0	0.5 (1/199)	Headache Throat irritation Nausea Paresthesia GI complaints
Schachtel 2014 ³⁰	24 h	25.7 (26/101) ^c	19.6 (19/97)	3.0 (3/101) ^{ce}	1.0 (1/97) ^e	1.0 (1/101) ^c	1.0 (1/97)	1.0 (1/101)	0	Headache Throat irritation
	7 days ⁱ	33.7 (34/101) ^c	28.9 (28/97)	3.0 (3/101) ^{ce}	2.1 (2/97) ^e	1.0 (1/101) ^c	1.0 (1/97)	1.0 (1/101)		
Blagden 2002 ³¹	7 days	44.8 (103/230) ^d	31.0 (71/228)	30.9 (71/230) ^d	19.7 (45/228)	5.3 (5/95) ^f	10.6 (7/66) ^f	9.6 (22/230) ^c	7.0 (16/228)	Taste perversion Nausea Diarrhea Abdominal pain Paresthesia

(Continued)

Table 7 (Continued).

Reference	Reporting Period	Patients Reporting TEAEs % (n/N)		Patients Reporting Drug-related AEs % (n/N)		Patients Reporting Severe AEs ^b % (n/N)		Discontinuations Due to AEs % (n/N)		Key AEs
		Flurb	Placebo	Flurb	Placebo	Flurb	Placebo	Flurb	Placebo	
Benrimoj 2001 ³²	5 days	51.6 (66/128) ^d	37.5 (48/128)	43.8 (56/128) ^d	28.1 (36/128)	3.8 (3/80) ^f	7.0 (3/43) ^f	0	0	Taste perversion Headache Dizziness Paresthesia Nausea
Watson 2000 ²²	4 days	39.5 (51/129) ^d	23.3 (30/129)	48.1 (37/77) ^g	19.1 (9/47) ^g	0	0	0	0	Taste perversion Paresthesia Dry mouth Nausea
de Looze 2016, de Looze 2018 ^{33,34}	3 h	6.8 (17/249) ^c	3.1 (8/256)	NR	NR	NR	NR	0	0	Headache Throat irritation Abdominal discomfort Dyspepsia
	3 days ⁱ	12.4 (31/249) ^c	8.2 (21/256)	6.8 (17/249) ^h	3.5 (9/256) ^h	NR	NR	0	0	
Radkova 2017, ²⁶ Burova 2018 ²⁵	3 days ^j	39.8 (175/440)	NA	3.0 (13/440)	NA	0	NA	0	NA	Throat irritation Dyspepsia Malaise Cough Hiccups Glossodynia Hypoesthesia
Russo 2013 ³⁸	7 days	23.1 (43/186) ^c	29.4 (55/187)	NR	NR	0	0	0	0	Headache Coughs Chills Pyrexia
Uztüre 2014 ⁴¹	24 h	NR	NR	NR	NR	NR	NR	NR	NR	
Aydin 2014 ⁴⁰	24 h	NR	NR	NR	NR	NR	NR	NR	NR	

Notes: ^aWhere more than one dose of flurbiprofen was studied, only data for the 8.75 mg dose are included. ^bNo severe AEs reported with flurbiprofen; ^cp=non-significant vs placebo; ^dp=significant vs placebo. ^eGI AEs related to study treatment. ^fPercentage (n/N) of drug-related AEs. ^gPercentage (n/N) of all TEAEs. ^hPossibly or probably related to study medication; no AEs were assessed as definitely related to study medication; ⁱCumulative, including 24-h data; ^jData for lozenge and spray combined.

Abbreviations: AE, adverse event; Flurb, flurbiprofen; GI, gastrointestinal; NA, not applicable; NR, not reported; TEAE, treatment-emergent AE.

providing patients and HCPs with the option to select the most appropriate formulation for the individual without compromising on efficacy. Moreover, data have demonstrated that flurbiprofen is effective even in patients with more severe or painful symptoms,^{29,35} who are more likely to visit their doctor and more likely to take antibiotics.⁴ Although these patients with more severe symptoms might be expected to be more resilient to the pharmacological effects of low dose (8.75 mg) flurbiprofen, studies demonstrated that the beneficial effects were actually similar or more pronounced in these patients compared with the overall study population.^{29,35}

The reviewed studies confirm the fast onset of symptomatic relief with flurbiprofen, beginning as early as 1–2 min post-dose.^{17,25,38} The demulcent activity of lozenges provides a rapid soothing effect (“active placebo”) as soon as they are sucked and allows a high initial deposition of active ingredient in the mouth and throat. The spray formulation delivers a full dose immediately at the site of pain and inflammation, coating the posterior pharynx.²⁴ This early onset of relief was most apparent in studies that employed a short time interval between assessments (eg 2 min), and initial assessment within 1–2 min after flurbiprofen administration.^{17,25,38} The data reviewed also demonstrate that “clinically meaningful” relief attributable to the anti-inflammatory effects of flurbiprofen occurs rapidly (from around 12 min post-dose)¹⁷ and is sustained for up to 4–6 h (the last time point assessed after a single dose).^{17,30,32–34,37,38}

Sore throat lasts for around 3–7 days,¹¹ therefore, many patients will require repeated dosing to relieve ongoing symptoms. Seven of the nine studies included in this review reported data for single- and multiple-dose flurbiprofen, suggesting that flurbiprofen administered 3–6 hourly when required, up to five times a day for up to 7 days, continues to provide clinically relevant, long-lasting relief for those patients whose symptoms remain bothersome.^{29–31,34,36–38} Patients entering these studies may have had a sore throat that started up to 7 days previously; therefore, the “first 24-h” period may actually have been up to the seventh day of these patients’ symptoms. As acute sore throat is of limited duration, with over 80% improving within a week,¹⁰ this may explain why the differences between flurbiprofen and placebo over subsequent days did not reach statistical significance in all of the studies.^{30,31,38}

Despite the fact that antibiotics are ineffective against viruses,^{11,14} and therefore inappropriate for up to 80% of pharyngitis cases,¹⁰ antibiotic prescribing for this condition

remains commonplace in primary care.⁵ Current treatment guidelines advocate symptomatic relief of sore throat as first-line treatment; even in bacterial sore throat, antibiotics do not provide immediate or useful relief of symptoms, with half of patients still experiencing pain after 3 days.¹¹ Moreover, physicians face considerable challenges in the accurate diagnosis of bacterial sore throat, with misdiagnosis potentially leading to inappropriate antibiotic prescribing and antibiotic resistance.^{5,37} Shephard et al highlighted the unreliability of strep A diagnosis based on clinical findings, with an 86.9% false positive result for strep A based on diagnosis by clinical features alone.³⁷ Even using a rapid strep test, the study suggested that 23.9% of patients would have received antibiotics unnecessarily.³⁷ Given its proven efficacy at providing fast and long-lasting relief from sore throat, particularly in the first few days when symptoms are worst,^{12,13} flurbiprofen offers a useful first-line treatment option for symptomatic relief in patients with “uncomplicated” acute sore throat, thus helping to reduce unnecessary antibiotic prescribing. Studies confirm the efficacy of flurbiprofen in patients both with and without strep sore throat,^{26,28,35,37} although the analyses included in this review are limited by the relatively low incidence of strep A/C positive patients. As most strep sore throats will resolve naturally over time, flurbiprofen can be considered prior to a definitive diagnosis of strep A/C; with the single-dose effects lasting for 3–4 h in these patients, it is reassuring that more persistent, severe or worsening symptoms associated with strep throat are unlikely to be “masked”, allowing patients to seek further advice and potentially antibiotics if required.³⁷ Even when the symptoms and course of sore throat suggest that antibiotics may be warranted, flurbiprofen can be safely combined with antibiotic therapy to effectively relieve pain and other symptoms that antibiotics will not immediately alleviate.³¹

NSAIDs have been associated with gastrointestinal AEs, which have been shown to be dose related.¹⁹ However, use of the lowest single dose of flurbiprofen proven to be effective for the relief of sore throat (8.75 mg)^{22,27} means that flurbiprofen was well-tolerated across the reviewed studies, with a predominantly mild and transient AE profile similar to placebo in the majority of studies.^{17,28–30,33–38} Taste perversion was more common with flurbiprofen lozenge than placebo in three studies; the high incidence of this AE can be attributed to the outdated Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) terminology used to classify the event in these older studies.^{22,31,32} Taste perversion is considered to be related to patient acceptability rather

than tolerability and lasts only until dissolution of the lozenge is complete.^{22,31,32} However, as the reviewed studies observed that patients' ratings of satisfaction and overall treatment efficacy were significantly better with flurbiprofen treatment than with placebo, patient acceptability does not appear to be an issue.^{22,25,26,30–32,34,36,38}

The results of the two POST studies included in this review are consistent with the findings of previous studies confirming the efficacy of a preoperative, locally delivered NSAID for the prevention of POST.⁴⁵ A systematic review of clinical studies in adults undergoing elective surgery under general anesthesia found that the topical NSAID benzydamine significantly decreased the incidence of POST compared with nonanalgesic controls; however, POST severity was not significantly reduced in this comparison.⁴⁵ Benzydamine was also associated with a significant reduction in the incidence of POST when compared with lidocaine.⁴⁵

In conclusion, the studies included in this review confirm that single- and multiple-dose flurbiprofen 8.75 mg, locally administered in lozenge, spray or microgranule form, is a well-tolerated and effective first-line treatment option for the fast and long-lasting symptomatic relief of sore throat, including in patients with more severe symptoms, patients with confirmed strep A/C sore throat, and patients taking concomitant antibiotics. In addition, a single preoperative dose of flurbiprofen lozenge appears to be effective for preventing or reducing the severity of early POST in patients undergoing general anesthesia.

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