

# Infantile haemangioma: topical timolol

## Evidence summary

Published: 14 August 2015

[nice.org.uk/guidance/esuom47](https://www.nice.org.uk/guidance/esuom47)

## Key points from the evidence

The content of this evidence summary was up-to-date in August 2015. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#), [BNF for children \(BNFc\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

## Summary

Limited evidence from 2 small randomised controlled trials (RCTs) and several observational studies suggests that topical timolol reduces the redness of superficial haemangiomas and may reduce their size or volume, but the clinical significance of these changes is unclear. The number of adverse events seen in the studies was low. However, systemic absorption has been shown with timolol used topically to treat infantile haemangiomas and larger studies would be useful to provide more safety data.

**Regulatory status:** off-label. This topic was prioritised because there was a high volume of requests from the NHS.

Effectiveness	Safety
<ul style="list-style-type: none"> <li>• In a systematic review and meta-analysis of 9 studies of topical timolol for mainly superficial infantile haemangiomas (1 RCT and 8 observational studies, total n=279), response rates ranged from 47% (95% confidence interval [CI] 24% to 71%) to 100% (95% CI 59% to 100%) in the individual studies, with a meta-estimate of 83% (95% CI 65% to 93%). Response was defined as at least a 20% decrease in size, a 5% decrease in volume, or a significant improvement assessed visually by health care providers or care givers.</li> <li>• In a placebo-controlled RCT (n=41), there was no statistically significant difference in the volume of superficial haemangiomas with timolol at week 24, but scores for redness were different (p=0.003). The proportion of scores of 0 (no redness) was 47% with timolol and 6% with placebo. The proportion of scores of 2 (completely red) was 6% with timolol and 55% with placebo.</li> <li>• In a RCT comparing topical timolol with laser treatment (n=60), there was greater improvement in lesion growth or colour, and shorter treatment duration with timolol compared with laser treatment for superficial haemangiomas, but the degree of improvement of mixed haemangiomas was greater in the laser group.</li> </ul>	<ul style="list-style-type: none"> <li>• Adverse effects that could occur from systemic absorption of timolol include bradycardia, hypotension, bronchospasm, peripheral vasoconstriction, weakness and fatigue, sleep disturbance and hypoglycaemia. However, the number of adverse events seen in studies of topical timolol for infantile haemangiomas is low.</li> <li>• In a systematic review and meta-analysis of 9 studies of topical timolol (total n=279) there was 1 adverse event of sleep disturbance.</li> <li>• In a placebo-controlled RCT (n=41) mean heart rate and blood pressure did not differ between topical timolol and placebo and no cases of bradycardia or hypotension were seen.</li> <li>• In a RCT comparing topical timolol with laser treatment (n=60) shortness of breath and insomnia were reported in 1 child in the timolol group.</li> <li>• The RCTs excluded infants or children with wheezing or asthma, cardiac rhythm disturbances or heart disease.</li> </ul>

Patient factors	Resource implications
<ul style="list-style-type: none"> <li>• Topical timolol is available in a variety of formulations, mainly as eye drops or gels, which are applied directly to the surface of the haemangioma.</li> <li>• In the studies included in this review, topical timolol was applied between 1 and 5 times a day. <a href="#">Great Ormond Street Hospital</a> use the gel-forming eye drops solution, Timoptol-LA 0.5%, applied at a dose of 1 drop 3 times a day.</li> <li>• Topical timolol is generally well tolerated.</li> <li>• Most of the evidence for using topical timolol is for treating often small, superficial infantile haemangiomas.</li> </ul>	<ul style="list-style-type: none"> <li>• Timolol 0.5% eye drops solution is £1.30 for 1×5 ml and Timoptol-LA 0.5% gel-forming eye drops solution is £3.12 for 1×2.5 ml (<a href="#">Drug Tariff</a>, July 2015).</li> </ul>

## Introduction and current guidance

Infantile haemangiomas (commonly known as strawberry marks or naevi) are benign vascular lesions that typically appear during the first 4 to 6 weeks of life. They have a characteristic evolution with early rapid growth (proliferation), followed by a stabilisation period and a slow spontaneous involution. Infantile haemangiomas differ greatly in terms of size, location, risk of complication, rate of proliferation and involution, and results after involution, and treatment is therefore individualised. The [British Association of Dermatologists haemangioma of infancy](#) information leaflet states that most haemangiomas do not require treatment except in the following situations:

- If the haemangioma is particularly large or affects areas where resolution may be incomplete such as around the nose, lips or ears.
- If the haemangioma is ulcerating.
- If the haemangioma is interfering with important functions or development of the senses, such as feeding, breathing, hearing or vision.

Treatments, which are generally off-label, can include topical, oral, intravenous or intralesional corticosteroids, topical timolol, oral propranolol, laser treatment or surgery. Emollients, non-adherent dressings, pain relief and antibiotics may also be required.

In April 2014, an oral propranolol product, [Hemangiol 3.75 mg/ml oral solution](#), received a Europe-wide marketing authorisation for the treatment of proliferating infantile haemangioma requiring systemic therapy. Hemangiol has not been launched in the UK.

[Full text of introduction and current guidance.](#)

## *Product overview*

Timolol is a beta-blocker, which is used topically in eye drops to reduce raised intra-ocular pressure. In 2008, the beta-blocker propranolol was found to be effective at treating infantile haemangiomas, when taken orally. Since then topical treatment with propranolol or timolol has been investigated. There are no topical timolol preparations licensed for treating infantile haemangiomas, and the use of any topical timolol preparation for this condition would be off-label.

The product currently used off-label at Great Ormond Street Hospital to treat infantile haemangiomas is the gel-forming eye drops solution, [Timoptol-LA 0.5%](#), applied at a dose of 1 drop 3 times a day (Great Ormond Street Hospital: [treating small infantile haemangiomas with topical timolol](#)).

[Full text of product overview.](#)

## *Evidence review*

- A systematic review and meta-analysis of the efficacy and adverse effects of locally administered beta-blockers for treating mainly superficial infantile haemangiomas included 9 studies of topical timolol (1 RCT and 8 observational studies, total n=279; [Ovadia et al. 2015](#)). The included studies varied in their treatment protocols (concentration of timolol, frequency of application and duration of treatment) and in how they measured response to treatment. The authors of the systematic review calculated response rates for each of the included studies and combined these using random effects models. Response was defined as a clinically significant change in the haemangioma after treatment, which represented at least a 20% decrease in size, a 5% decrease in volume, or a significant improvement as visually assessed by health care providers or care givers. Response rates in the individual studies ranged from 47% (95% CI 24% to 71%) to 100% (95% CI 59% to 100%), with the meta-estimate being 83% (95% CI 65% to 93%).
- In the RCT included in the meta-analysis ([Chan et al 2013](#)), 41 infants with small, focal superficial haemangiomas that did not require systemic therapy, were not ulcerated and were not near mucosal surfaces were randomised to 1 drop of topical timolol 0.5% (n=19) or placebo

gel (n=22) applied twice daily. Response to treatment was assessed by estimating the volume of the haemangioma (based on measurements of its circumference) and scoring photographs of the haemangioma for redness (blinded to treatment allocation). There was no statistically significant difference in the volume of haemangiomas between the timolol group and the placebo group at any time point. In terms of relative reduction of size, at week 24, statistically significantly more haemangiomas had reduced in volume by at least 5% in the timolol group compared with the placebo group (60% compared with 11%,  $p \leq 0.04$ ). However, specialists involved in the production of this evidence summary have suggested that a 5% reduction in volume is unlikely to be clinically significant. No statistically significant difference in photograph score distribution was seen at baseline or 12 weeks, but there was a difference at 24 weeks ( $p=0.003$ ). At week 24 the proportion of scores of 0 (no redness) was 47% in the timolol group and 6% in the placebo group; and the proportion of scores of 2 (completely red) was 6% in the timolol group and 55% in the placebo group.

- An RCT of 60 children with superficial or mixed infantile haemangiomas ([Tawfik et al. 2015](#)) compared between 1 and 3 drops of topical timolol 0.5% ophthalmic solution applied twice daily (n=30) with 595-nm pulsed dye and 1064-nm Nd:YAG laser treatment given monthly (n=30). Response, defined as regression or cessation of growth, shrinkage or flattening of the lesion, or lightening of surface colour, was assessed by the blinded evaluation of photographs and a skin analysis camera system to measure average haemoglobin levels of lesions. The authors report that 'excellent improvement' of between 76% and 100% in the parameters studied was seen in 40% of the timolol group compared with 20% of the laser group (no statistical analysis). For superficial haemangiomas, they report that earlier regression was seen with timolol compared with laser treatment and the timolol group had a shorter treatment duration. However, the degree of improvement of mixed haemangiomas was greater in the laser group.
- The largest prospective study of topical timolol for the treatment of infantile haemangiomas ([Yu et al 2013](#)) included 124 infants with cutaneous superficial haemangiomas. Of these, 101 received topical 0.5% timolol drops applied 3 times a day, with erythromycin ointment applied around the lesion to stop the drops from leaking. The other 23 infants underwent observation only. Response was evaluated from photographs with changes in colour, size and texture recorded. At 4 months, timolol was ineffective in 8 patients (8%), controlled the growth of the haemangioma in 36 patients (36%) and promoted regression in 57 patients (56%). Complete regression was seen in 12 patients who stopped receiving the drug and showed no relapse during the next 3 to 5 months follow-up. In the observation group, the lesion continued to grow in 15 patients (65%), 7 patients (30%) had controlled growth and 1 patient (4%) had regression.

- The largest retrospective cohort study of topical timolol for the treatment of infantile haemangiomas ([Chakkittakandiyil et al. 2012](#)) included 73 infants treated with timolol 0.1% (11/73) or 0.5% (62/73) gel-forming solution applied twice daily for a mean of 3.4±2.7 months. Of the 62 patients for whom data were available, 46 (74%) had superficial haemangiomas, 14 (23%) had mixed haemangiomas and 2 (3%) had deep haemangiomas. None of the haemangiomas were ulcerated. Results were evaluated by rating photographs using a visual analogue scale (VAS). The VAS used a 100 mm scale on which -100 mm represented a doubling in the size and extent of the lesion, 0 represented no change and +100 mm represented complete shrinkage, with 5 mm reflecting a 10% change. At the last follow-up visit, the mean improvement in the appearance of the haemangioma from baseline was 45±29.5%.
- If absorbed systemically, timolol can cause the same types of cardiovascular, pulmonary and other adverse reactions seen with other beta-blockers. Systemic absorption has been shown with timolol used topically to treat infantile haemangiomas. However, the actual number of adverse events seen in studies of topical timolol for the treatment of infantile haemangiomas is low. In the systematic review and meta-analysis ([Ovadia et al. 2015](#)), 1 adverse effect was reported across the 9 studies of topical timolol (total n=279). This was sleep disturbance in 1 infant in the retrospective study by [Chakkittakandiyil et al. 2012](#). The other studies reported no local or systemic adverse effects. In the placebo-controlled RCT by [Chan et al. 2013](#), mean heart rate, systolic blood pressure and diastolic blood pressure did not differ between treatment with topical timolol or placebo and no cases of bradycardia or hypotension were reported. In the RCT comparing topical timolol with laser treatment ([Tawfik et al. 2015](#)), shortness of breath and insomnia were reported in 1 patient in the timolol group. In both RCTs, infants or children with wheezing or asthma, cardiac rhythm disturbances or heart disease were excluded.
- Overall, limited high-quality evidence was found that investigated how effective topical timolol is for the treatment of infantile haemangiomas. Only 2 small RCTs were identified (n=41 and n=60) along with observational studies. The systematic review and meta-analysis ([Ovadia et al. 2015](#)) provides a useful summary of the efficacy and safety of topical timolol for treating mainly superficial infantile haemangiomas. However, it has several limitations inherent in the methodology which combines results from 1 RCT and 8 observational studies (n=7 to 101) which varied in their treatment protocols and in how they measured response to treatment. There is no validated assessment for treatment response in infantile haemangiomas, and it is difficult to evaluate whether the responses seen in the studies are clinically significant. All the studies included in this evidence summary used different scoring systems to measure response. The studies are also too small to analyse any rare adverse events.

- Most of the evidence for using topical timolol is in the treatment of small, superficial infantile haemangiomas. Specialists have suggested that topical timolol may offer an alternative to using oral propranolol in these cases, if the clinician and the parents choose to treat the haemangioma. However, it may also be appropriate to choose not to treat such haemangiomas. Neither topical timolol nor most oral propranolol preparations are licensed for treating infantile haemangiomas.

[Full text of evidence review.](#)

## *Context and estimated impact for the NHS*

Timolol 0.5% eye drops solution is £1.30 for 1×5 ml. Timoptol-LA 0.5% gel-forming eye drops solution is £3.12 for 1×2.5 ml ([Drug Tariff](#), July 2015).

No estimate of the current use of off-label topical timolol for treating infantile haemangioma is available.

[Full text of context and estimated impact for the NHS.](#)

## *Information for the public*

A [plain English summary](#) is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for parents or carers of infants with haemangiomas who are thinking about trying topical timolol treatment.

### **About this evidence summary**

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance.**

## Full evidence summary

### *Introduction and current guidance*

Infantile haemangiomas (commonly known as strawberry marks or naevi) are benign vascular lesions that typically appear during the first 4 to 6 weeks of life. Superficial haemangiomas are usually a raised, bright red area of skin, which may appear initially as a small area of pale skin on which a red spot develops. Deep haemangiomas may appear bluish in colour and are sometimes not noticeable for the first few weeks after birth, only appearing as a swelling as the haemangioma grows. Infantile haemangiomas have a characteristic evolution with early rapid growth (proliferation), followed by a stabilisation period and a slow spontaneous involution. The proliferative growth phase is generally completed by 6 to 10 months of age. Most haemangiomas will have disappeared completely by the age of 5 to 7 years, with large haemangiomas possibly continuing to get smaller until the child is about 8 to 10 years old. Most infantile haemangiomas have an uncomplicated clinical course, but around 12% are complex and require referral to specialists for consideration of treatment ([Great Ormond Street Hospital for Children haemangioma information](#) and [European Public Assessment Report \[EPAR\]: Hemangiol](#) [an oral propranolol product which has a Europe-wide marketing authorisation for infantile haemangioma but which has not been launched in the UK]).

Infantile haemangiomas differ greatly in terms of size, location, risk of complication, rate of proliferation and involution, and results after involution, and treatment is therefore individualised. The [British Association of Dermatologists haemangioma of infancy](#) information leaflet states that most haemangiomas do not require treatment except in the following situations:

- If the haemangioma is particularly large or affects areas where resolution may be incomplete such as around the nose, lips or ears.
- If the haemangioma is ulcerating.
- If the haemangioma is interfering with important functions or development of the senses, such as feeding, breathing, hearing or vision.

Treatments, which are generally off-label, can include topical, oral, intravenous or intralesional corticosteroids, topical timolol, oral propranolol, laser treatment or surgery. Emollients, non-adherent dressings, pain relief and antibiotics may also be required.

In April 2014, an oral propranolol product, [Hemangiol 3.75 mg/ml](#) oral solution, received a Europe-wide marketing authorisation for the treatment of proliferating infantile haemangioma



requiring systemic therapy. Hemangiol has not been launched in the UK and the manufacturer has no plans for a UK launch in the immediate future (personal communication Pierre Fabre Ltd, February 2015). However, it is available through specialist import companies. Several other oral propranolol products are readily available in the UK, including [Syprol oral solution 5mg / 5ml](#). Use of these for infantile haemangioma would be off-label.

The [British Association of Dermatologists haemangioma of infancy](#) information leaflet states that oral propranolol is now often the first choice when treatment is needed to stop haemangiomas at critical sites from enlarging and encourage them to shrink. The Great Ormond Street Hospital: [treating small infantile haemangiomas with topical timolol](#) information states that topical application of timolol is only used for small haemangiomas.

Topical timolol is available in a variety of formulations, mainly as eye drops which are licensed to reduce raised intra-ocular pressure. The topical timolol product currently used off-label at Great Ormond Street Hospital to treat infantile haemangiomas is the gel-forming eye drops solution, [Timoptol-LA 0.5%](#). The Great Ormond Street Hospital: [treating small infantile haemangiomas with topical timolol](#) information states this gel-forming solution is used as it is easier to apply to the skin. Parents are advised to apply 1 drop 3 times a day directly to the haemangioma and carefully spread it with their finger to cover the surface of haemangioma. Treatment is continued for up to 6 months or 1 year.

In a survey of 149 dermatologists in the USA ([Kumar et al. 2015](#)), the most common reasons clinicians chose to use topical timolol for the treatment of infantile haemangiomas were superficial haemangioma (97%), sensitive location such as the face (59%), family declined oral propranolol (44%), waiting to start propranolol (44%) and tapering off propranolol (29%).

## *Product overview*

### **Drug action**

Timolol is a beta-adrenoceptor blocking drug (a beta-blocker), which is used topically in eye drops to reduce raised intra-ocular pressure. In 2008, the beta-blocker propranolol was found to be effective at treating infantile haemangiomas, when taken orally. Since then topical treatment with propranolol or timolol preparations has been investigated ([Ovadia et al. 2015](#)). The Great Ormond Street Hospital information on [treating small infantile haemangiomas with topical timolol](#) states that topical timolol reduces the blood flow through haemangiomas, and more research is needed to confirm exactly how timolol works.

## Regulatory status

There are numerous topical timolol eye drop preparations available, which are licensed to reduce raised intra-ocular pressure in various conditions including ocular hypertension and glaucoma. There are no topical timolol preparations licensed for treating infantile haemangiomas, and the use of any topical timolol preparation for this condition would be off-label.

In line with the [guidance from the General Medical Council \(GMC\)](#), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using topical timolol outside its authorised indications.

## Cost

Timolol 0.5% eye drops solution is £1.30 for 1×5 ml. Timoptol-LA 0.5% gel-forming eye drops solution is £3.12 for 1×2.5 ml ([Drug Tariff](#), July 2015).

## Evidence review

This evidence summary is based on a systematic review and meta-analysis of mostly observational studies of locally administered beta-blockers for infantile haemangiomas, 2 small [randomised controlled trials](#) (RCTs) of topical timolol for infantile haemangiomas (1 placebo-controlled and 1 versus laser treatment) and the largest [observational studies](#) that provide the best available evidence for using topical timolol in this condition.

## Clinical effectiveness

A systematic review and meta-analysis of the efficacy and adverse effects of locally administered beta-blockers for treating infantile haemangiomas included 17 studies (18 comparisons, n=554; [Ovadia et al. 2015](#)). These studies mainly focused on superficial haemangiomas, with several studies excluding children with deep haemangiomas in anticipation of decreased efficacy. Three studies investigated intralesional propranolol, 6 studies investigated topical propranolol and 9 studies investigated topical timolol.

The sample size of the 9 included studies of topical timolol ranged from 7 to 101 (total n=279). The ages of children ranged from 2.1±0.8 months to 15.5±5.6 months and the duration of treatment in the studies was between 1 and 30 weeks. There was 1 RCT ([Chan et al. 2013](#)), 6 prospective observational studies (including [Yu et al. 2013](#)) and 2 retrospective observational studies (including [Chakkittakandiyil et al. 2012](#)). The treatment protocols varied in the studies with respect to the strength of timolol used, the application frequency and the duration of treatment. The highest

strength formulation used was 0.5% timolol, with application frequencies between 1 and 5 times daily.

The authors calculated response rates for each of the included studies and combined these using random effects models for each treatment group. Response to treatment was defined as a clinically significant change in the haemangioma after treatment, based on the methods reported in the included studies: at least a 20% decrease in size, a 5% decrease in volume, or a significant improvement as visually assessed by health care providers or care givers. No response was defined as patients reported to have poor response to treatment, no change in or stable haemangiomas, controlled growth or progression of haemangiomas or patients who were switched to systemic treatment.

Response rates in the individual studies of topical timolol ranged from 47% (95% confidence interval [CI] 24% to 71%) to 100% (95% CI 59% to 100%), with the meta-estimate being 83% (95% CI 65% to 93%). The rate of complete resolution of haemangiomas was reported in only a few studies and was lower than these rates. Prospective studies had a lower response rate than retrospective studies; 72% (95% CI 53% to 86%) compared with 97% (95% CI 84% to 99%) respectively ( $p < 0.01$ ). Results from studies including mixed or deep haemangiomas suggested topical timolol was less effective for these haemangiomas than for superficial haemangiomas.

## Randomised controlled trials

The RCT included in the meta-analysis ([Chan et al 2013](#)) was conducted in a single children's hospital in Australia. A total of 41 infants aged between 5 and 24 weeks with small, focal superficial haemangiomas that did not require systemic therapy, were not ulcerated and were not near mucosal surfaces were included. Infants with wheezing, cardiac rhythm disturbances or congenital heart disease were excluded. Infants were randomised to timolol 0.5% gel ( $n=19$ ) or placebo gel ( $n=22$ ) by the clinical trials pharmacist using a method of minimisation; both the parents and the physicians assessing the response were blinded to treatment allocation. Parents were instructed to apply 1 drop of gel twice daily to the surface of the haemangioma and to rub it in gently.

Response to treatment was assessed by estimating the volume of the haemangioma (based on measurements of its circumference) at weeks 0, 1, 2, 3, 4, 8, 12, 16, 20 and 24; and scoring photographs of the haemangioma at weeks 0, 12 and 24. Scoring was 0 if no redness was seen, 1 if the haemangioma was approximately 50% red and 2 if it was completely red. Safety was assessed by measuring heart rate and blood pressure at several time points.

There was no statistically significant difference in the volume of haemangiomas between the timolol group and the placebo group at baseline or at any time point. In terms of relative reduction of size, statistically significantly more haemangiomas had reduced in volume by at least 5% in the timolol group compared with the placebo group at weeks 8, 20 and 24 ( $p \leq 0.04$ ). At week 24, 9 (60%) of the 15 infants in the timolol group that were still in the trial (4 had dropped out) had haemangiomas that had reduced in volume by at least 5%. This compared with 2 (around 11%) of the 17 or 18 infants (different figures for the number of infants that dropped out are given in different tables in the paper) in the placebo group. However, a 5% reduction in volume is unlikely to be clinically significant. The efficacy of topical timolol appeared to be more pronounced in smaller lesions. For haemangiomas with a baseline volume of less than  $100 \text{ mm}^3$ , the relative change in volume was statistically significantly less in the timolol group compared with the placebo group from week 8 onwards ( $p < 0.003$ ).

No statistically significant difference in photograph score distribution was seen at baseline or 12 weeks, but there was a difference at 24 weeks ( $p = 0.003$ ). At week 24 the proportion of scores of 0 (no redness) was 47% in the timolol group and 6% in the placebo group; and the proportion of scores of 2 (completely red) was 6% in the timolol group and 55% in the placebo group.

Topical timolol has been compared with laser treatment in an RCT conducted at a single centre in Egypt ([Tawfik et al. 2015](#)). Sixty children with superficial or mixed infantile haemangiomas were randomised using a coin toss method to timolol 0.5% ophthalmic solution to be applied topically ( $n = 30$ ) or dual wavelength 595-nm pulsed dye and 1064-nm Nd:YAG laser ( $n = 30$ ). Children were excluded if they had asthma, cardiac rhythm disturbances or heart failure. The dose of timolol varied according to the size and depth of the haemangioma; between 1 drop and 3 drops were rubbed gently onto the surface of the haemangioma twice daily for a mean of  $4.0 \pm 1.1$  months. Laser treatment was given monthly for a mean of  $5.5 \pm 0.9$  months (4 to 6 sessions).

Treatment response, defined as regression or cessation of growth, shrinkage or flattening of the lesion, or lightening of surface colour, was assessed clinically by the blinded evaluation of photographs and objectively by using a skin analysis camera system to measure average haemoglobin levels of lesions. The authors report that 'excellent improvement' of between 76% and 100% in the parameters studied was seen in 40% of the timolol group compared with 20% of the laser group (no statistical analysis). For superficial haemangiomas, they report that earlier regression was seen with timolol compared with laser treatment and the timolol group had a shorter treatment duration. However, the degree of improvement of mixed haemangiomas was greater in the laser group.

## Observational studies

The largest prospective study of topical timolol for the treatment of infantile haemangiomas was conducted in a single hospital in China (Yu et al 2013). A total of 124 infants aged 12 months or less with cutaneous superficial haemangiomas ( $\leq 3$  mm in thickness) were included. Infants with bronchial asthma, sinus bradycardia and second- or third-degree atrioventricular block were not excluded from the study. Of the 124 infants 101 received topical 0.5% timolol drops applied to the surface of the haemangioma 3 times a day, with erythromycin ointment applied around the lesion to stop the drops from leaking. The other 23 infants underwent observation only.

The haemangiomas were photographed once a week and changes in colour, size and texture recorded, along with any adverse effects. Response was evaluated at 1-week and 4-month follow-up examinations based on 3 categories of response compared with baseline: ineffective (the lesion continued to grow), controlled growth (the lesion stopped growing but showed no significant change in size, colour or texture) or promoted regression (the lesion became smaller, softer and lighter in colour).

At 4 months, timolol was ineffective in 8 infants (8%), controlled growth in 36 infants (36%) and promoted regression in 57 infants (56%). Complete regression was seen in 12 patients who stopped receiving the drug and showed no relapse during the next 3 to 5 months follow-up. The percentage of infants with regression was higher in infants aged less than 6 months (64% [46/72]) compared with those aged more than 6 months (38% [11/29];  $p < 0.05$ ).

Compared with the observational group, statistically significantly more infants receiving timolol had regression ( $p < 0.05$ ), or controlled growth or regression ( $p < 0.05$ ). In the observation group, the lesion continued to grow in 15 infants (65%), 7 infants (30%) had controlled growth and 1 infant (4%) had regression.

The largest retrospective cohort study of topical timolol for the treatment of infantile haemangiomas included 73 infants from 5 hospitals in Canada, the USA and Australia (Chakkittakandiyil et al. 2012). Infants (median age 4.3 months) were included if they were treated with timolol 0.1% (11/73) or 0.5% (62/73) gel-forming solution (which was applied twice daily without occlusion) and had photographic documentation of the haemangioma and at least 1 follow-up visit. Of the 62 infants where data was available, 46 (74%) had superficial haemangiomas, 14 (23%) had mixed haemangiomas and 2 (3%) had deep haemangiomas. None of the haemangiomas were ulcerated.

Infants were treated for a mean of  $3.4 \pm 2.7$  months. Results were evaluated by rating photographs using a visual analogue scale (VAS). The VAS used a 100 mm scale on which -100 mm represented a doubling in the size and extent of the lesion, 0 represented no change and +100 mm represented complete shrinkage, with 5 mm reflecting a 10% change. At the last follow-up visit, change in the appearance of the haemangioma from baseline, as evaluated by 1 or more of the investigators who rated all photographs, was a mean improvement of  $45 \pm 29.5\%$  on the VAS. In exploratory analyses, treatment duration greater than 3 months compared with less than 3 months, 0.5% timolol compared with 0.1% timolol and superficial compared with deep haemangiomas were possible predictors of a favourable treatment response.

A further retrospective study from 1 hospital in Korea ([Park et al. 2014](#)) reviewed 61 children who had received topical timolol only and 41 children who had received topical timolol plus pulsed dye laser therapy as indicated. Children had superficial infantile haemangiomas which were not severe enough to require oral propranolol. Topical timolol was applied twice daily as 1 drop of 0.5% gel per  $\text{cm}^2$  onto the surface of the haemangioma and treatment continued for between 2 and 24 months. Adjunctive laser treatment was given to children who had marginal protrusion and gross disfiguring atrophy or showed worse response to topical treatment after 1 to 2 months.

Response to treatment was assessed by 2 dermatologists who compared baseline and follow-up photographs with respect to the colour, size, consistency and thickness of lesions on a score of 0 to 4 (where 0 represented no improvement, 1 represented an improvement of 0–24%, 2 was an improvement of 25–49%, 3 was an improvement of 50–74% and 4 was an improvement of 75–100%). The mean change in score from baseline to the last visit was 1.88 in the timolol group (a 47% change from baseline) and 2.66 in the timolol plus laser group (a 67% change from baseline;  $p=0.018$ ), suggesting adjunctive pulsed dye laser was beneficial. However, the two treatment groups differed in terms of lesion characteristics and response to initial topical treatment.

## Safety and tolerability

Timolol is a beta-blocker, which when used as an ophthalmic solution in the eyes can be absorbed systemically. The summary of product characteristics for [Timoptol-LA 0.5%](#) warns that the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-blockers may occur when timolol used in the eyes is absorbed systemically, although the incidence of systemic adverse reactions after topical administration in the eyes is lower than for systemic administration. Ophthalmic solutions of timolol used in the eyes are contraindicated in people with reactive airway disease including asthma or a history of asthma, severe chronic obstructive pulmonary disease; sinus bradycardia, sick sinus syndrome sino-atrial block, second- or third-degree atrioventricular block, overt cardiac failure and cardiogenic shock. Adverse effects

that could occur from systemic absorption include bradycardia, hypotension, bronchospasm, peripheral vasoconstriction, weakness and fatigue, sleep disturbance and hypoglycaemia.

Systemic absorption has also been shown with timolol used topically to treat infantile haemangiomas. In a study by Weibel et al. 2012, in 24 infants (aged 2 to 35 weeks) with small proliferating infantile haemangiomas who had urine analysis after timolol 0.5% gel was applied twice daily with no occlusion, 20 tested positive for the detection of timolol. Serum levels were measured in 4 infants resulting in a median value of 0.16 micrograms/L. The authors report that these levels are lower than for ophthalmic administration, but caution that care is still required particularly if topical timolol is being considered for extensive use in very young infants. A commentary by [McMahon et al. 2012](#) also cautions that using timolol near or on mucosal surfaces (such as eye, mouth or anus) or thinner skin sites (such as perineum) or in areas of haemangioma ulceration may further augment systemic absorption.

The actual number of adverse events seen in studies of topical timolol for the treatment of infantile haemangiomas are, however, very low, and the Great Ormond Street Hospital information: [treating small infantile haemangiomas with topical timolol](#) states that topical administration of timolol is safe and side effects are extremely rare.

In the systematic review and meta-analysis of locally administered beta-blockers ([Ovadia et al. 2015](#)), 1 adverse effect was reported across the 9 studies of topical timolol (total n=279). This was sleep disturbance in 1 infant in the retrospective study by [Chakkittakandiyil et al. 2012](#) (see below). The other studies reported no local or systemic adverse effects.

In the placebo-controlled RCT by [Chan et al. 2013](#), infants were excluded if they had haemangiomas near mucosal surfaces (where systemic absorption is likely to be greater) or they had wheezing, cardiac rhythm disturbances or congenital heart disease. Heart rate and blood pressure were measured before treatment was given, 1 hour after the first treatment was given and at every visit thereafter. Mean heart rate, systolic blood pressure and diastolic blood pressure did not differ between treatment with 1 drop of topical timolol 0.5% gel applied twice daily or placebo (p=0.81 for heart rate, p=0.28 for systolic blood pressure and p=0.40 for diastolic blood pressure), and no cases of bradycardia or hypotension were reported. Of 19 infants in the topical timolol group, 4 dropped out of the trial. This was because of a risk of ulceration in 2 patients and lack of efficacy noted by parents in 2 patients. All 4 of these infants went on to receive oral propranolol. In the placebo group, 5 out of 22 infants dropped out of the trial; 2 because of a risk of ulceration and 1 who developed a new haemangioma (all of who went on to receive propranolol); 1 infant was withdrawn voluntarily and 1 was transferred to another centre.

In the RCT comparing 1 to 3 drops of topical timolol 0.5% ophthalmic solution applied twice daily with laser treatment ([Tawfik et al. 2015](#)), shortness of breath and insomnia were reported in 1 child out of 30 in the timolol group. There were no reports of itching or irritation in this group.

In the largest retrospective cohort study ([Chakkittakandiyil et al. 2012](#)), 1 adverse event of 'significant sleep disturbance necessitating treatment' was reported in 1 infant out of 73 who were treated with timolol 0.1% or 0.5% gel-forming solution applied twice daily. No skin-related adverse events such as burning, stinging or irritation were noted.

The authors of largest prospective study ([Yu et al. 2013](#)) stated that no adverse effects were reported in the 101 infants who received topical timolol 0.5% drops applied 3 times a day. No adverse effects were also reported in the retrospective study by [Park et al. 2014](#) who reviewed 61 patients who had received 1 drop of 0.5% timolol gel per cm<sup>2</sup> twice daily and 41 patients who had received topical timolol plus pulsed dye laser therapy.

In a survey of 149 dermatologists in the USA ([Kumar et al. 2015](#)), estimated to have treated more than 7500 infantile haemangiomas with topical timolol in the last 4 years, 92% of respondents who had used topical timolol did not note any clinically relevant adverse effects. However, 74% said they did not routinely monitor heart rate and blood pressure of infants being treated with topical timolol. Reasons given for checking heart rate and blood pressure were for infants less than 2 months old, premature infants, and when topical timolol was to be used on a large area. The authors of the survey suggest that topical timolol should be used with caution, especially in preterm infants, or if topical timolol is being used on large body areas, ulcerated surfaces or mucous membranes. Adverse effects were noted by 8% of respondents; these included skin irritation or dryness, worsening of ulceration, diarrhoea, bradycardia and 1 case of hypothermia.

## Evidence strengths and limitations

Limited high-quality evidence was found that investigated how effective topical timolol is for the treatment of infantile haemangiomas. Only 2 small RCTs were identified, therefore this evidence summary also includes the largest observational studies that provide the best available evidence.

A systematic review and meta-analysis of topical beta-blockers for infantile haemangiomas has also been published ([Ovadia et al. 2015](#)). This provides a useful summary of the efficacy and safety of topical timolol for treating mainly superficial infantile haemangiomas. However, it has several limitations inherent in the methodology which combines results from 1 RCT and 8 observational studies of topical timolol. The included studies (n=7 to 101) varied in their treatment protocols (concentration of timolol, frequency of application and duration of treatment) and in how they



measured response to treatment. The authors of the systematic review calculated response rates for each of the included studies and combined these using random effects models. However, individual study response rates varied greatly and had wide confidence intervals. Prospective studies had lower response rates than retrospective studies, suggesting possible bias in how patients were selected or how outcomes were defined. Publication bias may also have occurred.

The 2 RCTs had strengths in that they were randomised studies, and compared topical timolol with either placebo or laser therapy. In the placebo-controlled trial ([Chan et al. 2013](#)) both the parents and the physicians assessing the response were blinded to treatment allocation. In the trial comparing topical timolol with laser therapy ([Tawfik et al. 2015](#)), treatment response was assessed clinically by the blinded evaluation of photographs. Limitations include the relatively small number of participants included in the single-centre trials (n=41 and n=60), uncertainty over whether allocation was concealed, and a lack of standardised outcome measures. There is no validated assessment for treatment response in infantile haemangiomas and evaluating whether the responses seen in the trials are clinically significant is difficult. The trials used different scoring systems to measure response from photographs of the lesions. Commenting on the trial by Chan et al. 2013, specialists involved in the production of this evidence summary have questioned whether a 5% decrease in volume could have any clinical significance because it is unlikely to have any effect on the eventual cosmetic outcome of the haemangioma. They have also suggested that the main clinically significant outcome from this trial is the reduction in redness at 24 weeks. This occurs in untreated haemangiomas over time, but a more rapid reduction in redness may be an important outcome for parents.

In terms of the generalisability of the findings from the RCTs, in the placebo-controlled RCT, infants were included if they had small, focal superficial haemangiomas that did not require systemic therapy, were not ulcerated and were not near mucosal surfaces. Infants with wheezing, cardiac rhythm disturbances or congenital heart disease were excluded. The RCT comparing topical timolol with laser treatment included children with superficial or mixed infantile haemangiomas. Again children with asthma, cardiac rhythm disturbances or heart failure were excluded.

The 2 RCTs both used timolol preparations of the same strength, but the formulations and dosing regimens differed. In the Australian RCT by [Chan et al. 2013](#), 1 drop of timolol 0.5% gel was applied to the surface of the haemangioma twice daily. In the Egyptian RCT by [Tawfik et al. 2015](#), timolol 0.5% ophthalmic solution was used and between 1 and 3 drops were applied twice daily. The product currently used off-label at Great Ormond Street Hospital to treat infantile haemangiomas is the gel-forming eye drops solution, [Timoptol-LA 0.5%](#), and a dose of 1 drop 3 times a day is used (Great Ormond Street Hospital: [treating small infantile haemangiomas with topical timolol](#)).

The observational studies included in this evidence summary had more participants than the RCTs (n=73 and n=101). However, these studies are still too small to analyse rare adverse events, and they have limitations inherent in their non-randomised design. Variations in treatment protocols and how response was measured were also limitations of these studies.

Most of the evidence for using topical timolol is in the treatment of small, superficial infantile haemangiomas. Specialists have suggested that topical timolol may offer an alternative to using oral propranolol in these cases, if the clinician and the parents choose to treat the haemangioma. However, it may also be appropriate to choose not to treat such haemangiomas. Neither topical timolol nor most oral propranolol preparations are licensed for treating infantile haemangiomas.

## Context and estimated impact for the NHS

### Cost effectiveness

No cost-effectiveness studies were identified that assessed the use of off-label topical timolol for treating infantile haemangioma.

The table below gives costs for beta-blockers (topical timolol and oral propranolol) used for infantile haemangioma.

**Table 1 Costs of beta-blocker treatments for infantile haemangioma**

	Cost excluding VAT
Topical timolol	<p><u>Timoptol-LA 0.5% gel-forming eye drops solution 1×2.5 ml</u>: £3.12<sup>a</sup></p> <p>Timolol 0.5% eye drops solution 1×5 ml: £1.30<sup>a</sup></p>
Oral propranolol <sup>b</sup>	<u>Syprol 5 mg/5 ml oral solution 150 ml</u> : £12.50 <sup>c</sup>

<sup>a</sup> Costs taken from Drug Tariff, July 2015.

<sup>b</sup> In April 2014, an oral propranolol product, Hemangirol 3.75 mg/ml oral solution, received a Europe-wide marketing authorisation for the treatment of proliferating infantile haemangioma requiring systemic therapy. Hemangirol has not been launched in the UK and the manufacturer has no plans for a UK launch in the immediate future (personal communication Pierre Fabre Ltd, February 2015). However, it is available through specialist import companies. Several other oral propranolol products are readily available in the UK, including Syprol oral solution. Use of these for infantile haemangioma would be off-label.

<sup>c</sup> Costs taken from MIMS, July 2015.

## Current drug usage

No estimate of the current use of off-label topical timolol for treating infantile haemangioma is available.

## *Information for the public*

A [plain English summary](#) is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for parents or carers of infants with haemangiomas who are thinking about trying topical timolol treatment.

## *Relevance to NICE guidance programmes*

The use of topical timolol for treating infantile haemangioma is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme. There is currently no NICE guidance on the treatment of infantile haemangioma.

## *References*

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### *Development of this evidence summary*

The integrated process statement sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

### **Expert advisers**

Dr Mary Glover. Consultant Paediatric Dermatologist and Head of Clinical Service, Great Ormond Street Hospital, London

Dr Lindsay Shaw, Consultant in Adult and Paediatric Dermatology, University Hospitals Bristol and Great Ormond Street Hospital, London

### **Declarations of interest**

No relevant interests declared.

### About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance.**

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ISBN: 978-1-4731-1379-4