Public Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

(Phentolamine mesilate) Phentolamine mesilate

UK/W/0092/pdWS/001

Rapporteur:	United Kingdom
Finalisation procedure:	12th July 2016

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	See section VII
INN (or common name) of the active substance:	Phentolamine mesilate
Marketing authorisation holder:	See section VII
Pharmaco-therapeutic group (ATC Code):	Imidazoline derivatives, V03AB36.
Pharmaceutical form and strength:	Cartridge containing solution for injection: 400 micrograms/1.7ml

ABBREVIATIONS

AE	Adverse event
ATC	Anatomical, Therapeutic, Chemical
EC	European Commission
LA	Local anaesthetic
MAH	Marketing authorisation holder
mITT	Modified intention-to-treat
pFAB	Paediatric functional assessment battery
PL	Package leaflet
SmPC	Summary of product characteristics
UK	United Kingdom
W-B PRS	Wong-Baker Pain Rating Scale

I. EXECUTIVE SUMMARY

On 23rd February 2016, one marketing authorisation holder (MAH) submitted a completed paediatric study for phentolamine mesilate in accordance with Article 46 of Regulation (EC) No. 1901/2006, as amended, on medicinal products for paediatric use.

The study was a Phage 4, multi-centre, randomised, double-blinded, controlled study of phentolamine mesilate in 150 patients aged 2 to 5 years undergoing routine mandibular and maxillary dental procedures requiring the use of an intra-oral, sub-mucosal injection of catecholamine-containing local anaesthetic.

Phentolamine mesilate is licensed in the United Kingdom (UK), Italy France, Spain and Germany for the reversal of soft tissue anaesthesia (lip and tongue), and the associated functional deficits, arising from an intraoral submucosal injection of a local anaesthetic containing a catecholamine vasoconstrictor, following a routine dental procedure such as teeth cleaning, scaling and planning, cavity filling, and crowns.

Phentolamine mesilate is a competitive, short-acting, non-selective α1- and α2-adrenergic receptor blocker, which antagonises the vasoconstrictor effects of endogenous and exogenous catecholamines. This results in vasodilation and therefore increased local blood flow, with the aim of accelerating the return of normal sensation to soft tissues following completion of the dental procedure.

The SmPC contains posology for both adults and children.

The MAH stated that the submitted paediatric study supports the use of phentolamine mesilate for the indication described in the SmPC and does not change the benefit risk for phentolamine mesilate, and that there is no consequential regulatory action.

The MAH was asked for additional information on the size of the lidocaine cartridge cited in the SmPC on 11th May 2016 and responded on 12th May 2016.

Summary of outcome

- ☒ No change
- ☐ New study data
- ☐ New safety information
- ☐ Paediatric information clarified
- ☐ New indication

II. RECOMMENDATION

No SmPC and PL changes are proposed in this summary report as a result for this Article 46 submission.

However, the dosing schedule currently provided in section 4.2 is ambiguous with regard to the volume of local anaesthetic (lidocaine 2% with 1:100,000 adrenaline) that is referred to by the word “cartridge”. The MAH should submit a variation in accordance with Regulation (EC) No. 1234/2008 to update the SmPC dosing regimen with the volume in millilitres of local anaesthetic as posology reference, to replace the ambiguous term “cartridge”.

III. INTRODUCTION

On 23rd February 2016, one MAH submitted a completed paediatric study for phentolamine mesilate in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

(A short critical expert overview has also been provided.)

A short critical expert overview, the relevant literature references and the full, final study report were also provided.

The MAH stated that the submitted paediatric study supports the use of phentolamine mesilate for the indication described in the SmPC and does not change the benefit risk for phentolamine mesilate, and therefore there is no need for any regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical study

Phentolamine mesilate is a competitive, short-acting, non-selective α1- and α2-adrenergic receptor blocker, which antagonises the vasoconstrictor effects of endogenous and exogenous catecholamines. This results in vasodilation and therefore increased local blood flow, with the aim of accelerating the return of normal sensation to soft tissues following completion of the dental procedure.

Phentolamine mesilate is available as packs of 10 or 50 cartridges, with each cartridge containing phentolamine mesilate solution for injection 400 micrograms in 1.7ml. This formulation was used in the submitted study. This formulation is intended for adults and children over 6 years and weighing over 15 kg, according to the dosing schedule detailed in the SmPC:

Adult subjects
The recommended dose of phentolamine mesilate is based on the number of cartridges of local anaesthetic with vasoconstrictor administered:

Amount of LA administered [cartridge(s)]	Amount of phentolamine mesilate to be administered [cartridge(s)]	Dose of phentolamine mesilate [µg]
½	½	200
1	1	400
2	2	800

The maximum recommended dose is 2 cartridges (800 micrograms) of phentolamine mesilate.

Paediatric subjects
As for adult subjects, the recommended dose of phentolamine mesilate in paediatric subjects is based on the number of cartridges of local anaesthetic with vasoconstrictor administered.
The maximum dose to be administered should be determined based on the age and weight of the subject, as follows:

Age	Weight	Maximum amount of phentolamine mesilate [cartridge(s)]	Maximum dose of phentolamine mesilate [µg]
6-11 years	15-30 kg	½	200
6-11 years	> 30 kg	1	400
≥ 12 years	> 30 kg	2	800

The efficacy of phentolamine mesilate in children less than 6 years of age has not yet been established. Currently available data are described in section 5.1 and 5.2 but no recommendation on a posology can be made.

Rapporteur's comment:

Neither the current SmPC, nor the submitted study, specify the volumes in millilitres of a "cartridge" of local anaesthetic (lidocaine 2% with 1:100,000 adrenaline) used to select the required phentolamine posology. This needs to be clarified, as local anaesthetic solutions come in several formulations across the US and EU markets.

IV.2 Clinical aspects

1. Introduction

The MAH submitted a report for:

The study: "*A Phase 4, Multicenter, Randomized, Double-Blinded, Controlled Study of Phentolamine mesilate for Safety and Efficacy in Pediatric Dental Patients Undergoing Mandibular and Maxillary Procedures"*

2. Clinical study

"*A Phase 4, Multicenter, Randomized, Double-Blinded, Controlled Study of Phentolamine mesilate for Safety and Efficacy in Pediatric Dental Patients Undergoing Mandibular and Maxillary Procedures"*

- **Description**

A prospective, multi-centre US study of the safety and efficacy of phentolamine mesilate for reversal of local anaesthetic in paediatric dental patients undergoing routine dental procedures.

- **Methods**

- Objective(s)

  - Primary objective: To determine the safety and tolerability if phentolamine mesilate in patients 2-5 years of age.
  - Secondary objective: To determine if phentolamine mesilate accelerated the time to normal function and sensation of lip and tongue.

- Study design

  Prospective, randomised, double-blind, controlled clinical study.

- Study population /Sample size

  The study population was 150 male and female paediatric dental patients across seven different US centres, aged from 2 to 5 years and weighing at least 15kg, who were undergoing a routine dental procedure requiring the application of an intra-oral, sub-mucosal injection of local anaesthetic (specifically, lidocaine 2% with 1:100,000 adrenaline).

  The sample size was chosen on the basis of the primary objective of safety and tolerability, with the aim of being able to detect adverse events (AEs) estimated to occur at a rate of 3% in the population.

  Patients were randomised to treatment with phentolamine mesilate or sham injection, in a 2:1 allocation ratio, at the point of completion of the dental procedure and following confirmation of eligibility criteria (at least one abnormal Paediatric Functional Assessment Battery (pFAB) test (Table 3) and / or numbness of the relevant mouth quadrant).

Centralised randomisation was performed by authorised staff using an Interactive Voice Response System. Randomisation was stratified by location of the dental procedure (mandible or maxilla) and the amount of local anaesthetic used ($^1/_4$, ½ or 1 cartridge).

Rapporteur's comment:

The study is small in size. The applicant states that the study was not prospectively powered to detect statistically significant differences in efficacy measures.

Originally, 15 patients were to be recruited into each of the 2 and 3 year age groups. However, the sponsor did not enrol sufficient patients in these age groups, resulting in skewed distribution across age groups seen in Table 1:

Table 1. Subject Sample Distribution by Age, from final study report.

Age Group	Number of OraVerse Subjects	Number of Sham Subjects
2 years	10	5
3 years	10	5
4 year	40	20
5 years	40	20
Total	100	50
Total Study: 150 Subjects		

- Treatments

Investigators had the option to apply benzocaine 20% topical gel to provide local anaesthesia in advance of sub-mucosal injection of local anaesthetic and study drug. 98% of all patients received this. Lidocaine 2% with 1:10,000 adrenaline was administered to the relevant mouth quadrant prior to the dental procedure, as per the dosing schedule in Table 2. Supplemental injections of local anaesthetic were permitted to increase anaesthesia in the local area "*as long as they were not likely to contribute to soft tissue anaesthesia and were less than a total of 0.6ml*".

Investigators also had the option to use inhaled nitrous oxide. 80% of all patients received this.

Patients randomised to receive either:

- Phentolamine mesilate by submucosal injection of 400µg/1.7ml solution, at the same site as the local anaesthetic injection, administered in a 1:1 ratio with the volume of local anaesthetic received.
- A sham injection, performed without making an actual injection into the tissue.

The subject was blinded to the treatment received through use of visual barriers to obstruct their view of the preparation and administration of the study drug. A blinded observer was responsible for performing safety and efficacy assessments.

Table 2. Dose of Local Anaesthetic and Study Drug by Weight, from final study report

Subject's Weight (measured in kg)	Lidocaine/epinephrine Cartridge Amount	OraVerse Cartridge Amount (mg phentolamine mesylate)
≥ 10 kg to < 15 kg	¼	¼ (0.1 mg)
≥ 15 kg to < 30 kg	½	½ (0.2 mg)
≥ 30 kg	½ or 1	½ or 1 (0.2 or 0.4 mg)

Rapporteur's comment:

Benzocaine 20% topical gel has been reported to produce rapid-onset pain relief with duration of action varying from 15 minutes (according to the applicant) to >120 minutes. As 98% of all patients in the study received this topical anaesthesia, with similar proportions in the study drug and sham injection groups (97% vs 100%), it is unlikely to affect comparison between the treatment groups, provided that individual response to the topical pre-treatment can be assumed to be the same.

Supplemental local anaesthetic injections were given to similar proportions in the study drug and sham injection groups (12.1% vs 15.7%), but it is not reported how much supplemental injection each subject received. Supplemental injections were allowed "*as long as they were not likely to contribute to soft tissue anaesthesia and were less than a total of 0.6ml*", a qualifier which is confusing given the mechanism of action of local anaesthetic.

A sham injection served as the clinical comparator for the investigational product. This mimics the time, preparation and application of the study drug but, significantly, does not penetrate the tissue. Although the subject was visually blinded to the study treatment received, it is possible that they would still be able to determine this difference.

- Outcomes/endpoints

  The *primary endpoint* was safety and tolerability of phentolamine mesilate as measured by adverse events, vital signs, general and specific oral cavity assessments, nerve injury, and post-procedural requirement of analgesics for intraoral pain.

  The *secondary endpoints* were:
  - Safety and tolerability of phentolamine mesilate as measured by pain assessments using Wong-Baker Pain Rating Scale (W-B PRS), in patients aged 4 and 5 years of age, who were trainable in W-B PRS.
  - Efficacy of phentolamine mesilate as measured by time to normal sensation using pFAB scoring system, in patients aged 4 and 5 years of age, who were trainable in pFAB.
  - Efficacy of phentolamine mesilate as measured by time to normal sensation using standardised lip and tongue palpation procedure, in patients aged 4 and 5 years of age, who were trainable in palpation procedures.

Table 3. Paediatric Functional Assessment Battery (pFAB) Observer Rating Criteria

Function	Rating	Definition
Smiling, Speaking, Drinking	Normal	Normal for each function was defined as "same as" or "equivalent" to performance of test at baseline.
	Abnormal	Abnormal for each function was defined as "not normal" or "different" from baseline.
Drooling	Present	Presence of drooling was to be interpreted as "abnormal".
	Absent	Absence of drooling was to be interpreted as "normal".

Rapporteur's comment:

The safety endpoints studied are suitable to determine safety and tolerability of phentolamine mesilate in this population. A "worst-case approach" was followed in the event of missing AE data.

The efficacy endpoints studied all reflect time to restore normal sensation or function, but do not demonstrate the clinical relevance or benefit of this outcome for the patient (e.g. reduction in accidental oral injury post-procedure).

- Statistical Methods

  Descriptive statistics were provided to characterise the safety and tolerability of phentolamine mesilate verus sham injection.

  The safety analysis data sets were defined as:
  - Full safety set for *primary safety endpoint* (adverse events, vital signs, oral cavity assessments, nerve injury and post-procedural analgesia requirements) – all randomised patients administered study drug.
  - Modified intention-to-treat (mITT) set for *secondary safety endpoint* (W-B PRS score) – all randomised patients aged 4 and 5 years who were trainable in W-B PRS.

  Kaplan-Meier plots were used to report time to normal sensation of lip and tongue for each treatment group. Additionally, the stratified log-rank test (stratified by location of procedure to mandible or maxilla) was used to test the null hypothesis that the distributions of time to normal sensation were equal between phentolamine mesilate and sham injection groups, using two-sided significance level of $p<0.05$.

  The modified intention-to-treat data sets were defined as:
  - For *mITT pFAB set* – all randomised patients aged 4 and 5 years who were trainable in pFAB, had a normal pFAB at baseline and at least one abnormal pFAB function at completion of the dental procedure.
  - For *mITT lip sensation set* – all randomised patients aged 4 and 5 years who were trainable in lip palpation, had normal lip sensation at baseline and numbness of the relevant lip quadrant at completion of the dental procedure.

- For *mITT tongue sensation set* – all randomised patients aged 4 and 5 years who were trainable in tongue palpation, had normal tongue sensation at baseline and numbness of the tongue at completion of the dental procedure.

There were no planned or executed adjustments for other covariates during data analyses.

Missing data were not imputed, with the exception of missing W-B PRS and pFAB scores, where a last post-baseline observation carried forward (LOCF) method was used.

Rapporteur's comment:

The applicant's selection of modified intention-to-treat subgroups exposes the study to selection bias, by only including patients who are "trainable" in study assessments.

It is not clear if or how stratification by treatment centre or treatment dose (performed at the point of randomisation) were taken into account at the point of analysis.

- **Results**

- Recruitment/ Number analysed

150 patients were enrolled, randomised, treated and analysed; 99 randomised to phentolamine mesilate and 51 randomised to sham injection.

There was generally a good follow-up rate; with 5 "drop-outs" in the phentolamine mesilate treatment group (3 incomplete follow up, 1 withdrew consent, 1 withdrawn by investigator following a significant protocol violation) and none in the sham injection group. These 5 patients were not included in any analyses.

There were patients with partial data; 3 patients in the phentolamine mesilate group did not complete the study observations, 6 did not complete telephone follow-up and 2 did not complete in-clinic follow-up. In contrast, just 1 subject in the sham injection group had partial data because they did not complete telephone follow-up.

There were 11 reported major protocol deviations across the study. 6 of these protocol deviations involved in the informed consent process and were not expected to compromise the integrity of the data.

4 protocol deviations were made with respect to inclusion / exclusion criteria and 1 protocol deviation was related to study procedure (a subject in the sham injection group who was mistakenly penetrated with the needle). All 5 of these deviations might be expected to affect study results, and so these patients were included in safety and mITT data sets but excluded from per protocol analysis.

Rapporteur's comment:

The majority of patients received ½ cartridge of phentolamine mesilate, based on a weight of 15-30kg. Only 11 of 150 patients (7.3%) weighed 10-15kg and therefore received ¼ cartridge; only 6 of 150 patients (4%) weight >30kg and therefore received 1 cartridge.

- Baseline data

  Baseline characteristics of randomised patients were generally similar between the phentolamine mesilate and sham injection groups.

  A slightly higher proportion of patients in the sham injection group were in the lowest and highest weight brackets, and also reported a slightly higher rate of pre-existing medical conditions or surgical procedures and concomitant medications.

  Patients in both groups received the study drug or sham injection an average of 29 minutes after local anaesthetic, although there was a wide range for this across the study (11 to 58 minutes).

  The proportion of patients trainable in pFAB, W-B PRS and palpation procedures, and therefore included in the mITT analyses, were similar l between the phentolamine mesilate and sham injection groups.

Rapporteur's comment:

No specific analyses were performed to determine the effects of differing baseline rates of medical and surgical history, and concomitant medications, on the effect of phentolamine mesilate.

- Efficacy results

  mITT pFAB: analysis of 87 patients (incorporating 58.6% of the phentolamine mesilate and 56.9% of the sham injection groups, who were trainable and had at least one abnormal pFAB test following the procedure) showed a reduction in median time to recovery of normal function from 45 minutes to 31 minutes. Stratified log-rank test found this not statistically significant ($p = 0.0559$).

  mITT lip sensation: analysis of 108 patients (incorporating 71.7% of the phentolamine mesilate and 72.5% of the sham injection groups, who were trainable and reported a "numb" lip following the procedure) showed a reduction in median time to normal lip sensation from 109 minutes to 61 minutes. Stratified log-rank test showed this to be statistically significant ($p < 0.0001$).

  Sub-set analysis demonstrated a statistically significant ($p = 0.0074$) reduction in median time to normal lip sensation from 123 minutes to 68.5 minutes in the *mandibular* procedure group.

  Sub-set analysis demonstrated a statistically significant ($p = 0.0009$) reduction in median time to normal lip sensation from 105.5 minutes to 45 minutes in the *maxillary* procedure group.

  mITT tongue sensation: analysis of 53 patients (incorporating 36.4% of the phentolamine mesilate and 33.3% of the sham injection groups, who were trainable and reported a "numb" tongue following the procedure) showed a reduction in median time to normal tongue sensation from 91 minutes to 60 minutes. Stratified log-rank test found this not statistically significant ($p = 0.5719$).

Per protocol sensitivity analysis was performed on a group of 145 patients (excluding 5 patients with major protocol deviations). This gave similar trends for all outcomes except time to recovery of normal function as measured by pFAB, where the *per protocol* analysis did show the difference between groups to be statistically significant (p = 0.0327).

Kaplan-Meier plots of phentolamine mesilate vs sham injection in the mITT groups visually demonstrated a faster time to recovery of normal sensation of lip and tongue, and faster time to recovery of normal function as measured by pFAB.

- Safety results

There were no AEs that lead to death or study discontinuation and no serious adverse events.

In the full safety set of 150 patients, a total of 48 patients (32%) reported treatment-emergent AEs, of which 30 were deemed to be treatment-related. These rates were similar across the two groups and were mild to moderate in severity, with the exception of one severe adverse event, severe intraoral pain, was reported; this occurred in the sham injection group and was therefore considered unrelated to the study drug.

In the *mITT W-B PRS safety set* analysis of 119 patients (incorporating 79.8% of the phentolamine mesilate and 78.4% of the sham injection groups, who were trainable), scores of pain intensity were comparable between the two groups. However, the incidence of oral pain, both reported through W-B PRS and reported as an AE, was slightly higher in the phentolamine mesilate group (10.1%) than the sham injection group (3.9%).

The proportion of patients with clinically significant oral cavity assessments was similar between the two groups across all time points. There were no reports of nerve injury.

A higher proportion of patients in the phentolamine mesilate group than in the sham injection group were observed to show a decrease of >20mmHg in systolic blood pressure relative to prior to study drug (12.1% vs 5.9%); a decrease of >20mmHg in diastolic blood pressure relative to prior to the study drug (7.1% vs 2%); and an increase of >20 bpm in heart rate relative to prior to the study drug (10.1% vs 5.9%). All patients were asymptomatic and all effects were temporary and resolved without intervention.

A slightly higher proportion of patients in the sham injection group used additional analgesia for intraoral pain within the 48 hours following the procedure. However, the sham injection group started with a higher baseline rate of paracetamol use than the phentolamine mesilate group (5.9% vs 2.0%).

The telephone follow up data show that the proportion of patients reporting they bit their lip, cheek or tongue after leaving the dentist's office was similar across phentolamine mesilate and sham injection groups (6.1% vs. 4.9%). Similar data were produced in the in-clinic follow-up (3% vs 3.9%).

Rapporteur's comment:

It is not surprising that phentolamine mesilate was associated with a slightly higher incidence of oral pain post-procedure, as the reversal of local anaesthetic effects might be expected to produce this. Systemic effects on blood pressure and heart rate are also physiologically plausible based on the mechanism of action of phentolamine mesilate. However, both treatment groups showed the same trend in this regard, and it very likely that changes in blood pressure and heart rate in this clinical situation are also affected by stress and discomfort. It is important to note that all patients were asymptomatic with respect to blood pressure and heart rate changes.

Interestingly, there was no evidence of significant rates of accidental post-procedural oral injury in either group arising from anaesthesia of the oral soft tissues, despite this being the applicant's argument in favour of the benefit / risk balance of this product.

3. Discussion on clinical aspects and conclusion

- Safety

The primary objective of the study was to assess safety and tolerability of phentolamine mesilate in the paediatric population aged 2-5 years, when being used according to the indication already licensed in children 6 years and older. Overall, AEs were mild to moderate, similar between the groups and likely to be procedure-related rather than specifically study drug related. The slight increase in incidence of oral pain in the phentolamine mesilate group might be expected from the mechanism of action of the drug, which causes the local anaesthetic effect wear off more quickly. Although an increase in incidence was not associated with an increase in intensity of oral pain, this trend does call into question what the benefit of the study treatment is to the patient in clinical practice.

- Efficacy

This study was not prospectively powered to detect statistically significant differences in efficacy measures. The mITT analyses show a trend of reduced mean time to recovery of sensation and function with phentolamine mesilate vs sham injection, with demonstrable statistical significance in some sub-sets. However, the clinical relevance of this in terms of benefit to the patient is not established and was not explored in this study.

V. REQUEST FOR SUPPLEMENTARY INFORMATION

On 11th May 2016 the MAH was asked to clarify the size or volume of local anaesthetic (lidocaine 2% with 1:100,000 adrenaline) that is referred to in the SmPC and the submitted study by the word “cartridge”.

The MAH responded with the required information on 12th May 2016, and confirmed that the volume of local anaesthetic (lidocaine 2% with 1:100,000 adrenaline) that is referred to in the SmPC and the submitted study by the word “cartridge” is 1.7ml.

VI. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The data from the submitted study, assessed as part of the European work-sharing procedure under Article 46 of Regulation (EC) No. 1901/2006, are not sufficient to establish the benefit-risk balance for phentolamine mesilate use in paediatric patients under 6 years or weighing less than 30kg.

The current SmPC and the submitted study do not specify the size of a “cartridge” of local anaesthetic (lidocaine 2% with 1:100,000 adrenaline). This should be clarified for the purposes of the SmPC, as local anaesthetic solutions come in several formulations across the US and EU markets.

- **Recommendation**

No SmPC and PL changes are proposed in this summary report as a result for this Article 46 submission.

However, the dosing schedule currently provided in section 4.2 is ambiguous with regard to the volume of local anaesthetic (lidocaine 2% with 1:100,000 adrenaline) that is referred to by the word “cartridge”. The MAH should submit a variation in accordance with Regulation (EC) No. 1234/2008 to update the SmPC dosing regimen with the volume in millilitres of local anaesthetic as posology reference, to replace the ambiguous term “cartridge”.

VII. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Septodont Holding / France	OraVerse®	400 micrograms in 1.7ml	SOLUTION FOR INJECTION	PHENTOLAMINE MESILATE