Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

Pethidine Hydrochloride

Pethidine

IE/W/0014/pdWS/001

Rapporteur:	IE
Finalisation procedure (day 120):	25/09/2020

TABLE OF CONTENTS

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Pethidine
INN (or common name) of the active substance(s):	Pethidine Hydrochloride
MAH (s):	Sanofi Aventis
Pharmaco-therapeutic group (ATC Code):	NO2AB02
Pharmaceutical form(s) and strength(s):	50 mg

I. EXECUTIVE SUMMARY

SmPC and PL changes are proposed in sections 4.4 and 5.2.

Summary of outcome

☐ No change

☐ New study data:

☐ New safety information:

☒ Paediatric information clarified: Section 4.4 & 5.2, clarification of inter-subject variability in neonates and infants

☐ New indication:

II. RECOMMENDATION[1]

In response to a question from the Rapporteur as to how the product information was to be updated the company (Sanofi) responded as follows.

The company proposes to add the following Warning in section 4.4 (Special warnings and precautions for use) of the SmPC:

"Pethidine has a slower elimination rate and a larger inter-subject variability in neonates and young infants compared to older children and adults, which may lead to dose related reactions such as respiratory depression. If pethidine use is contemplated in neonates or young infants (up to 12 months), any potential benefits of the drug need to be weighed against the relative risk to the patient."

This text is acceptable to the Rapporteur and commenting Member States, but is only applicable for products that are approved in the specific age group.

In addition, the text below has been proposed (by a commenting Member State) to be added to section 5.2 (Pharmacokinetic properties) of the SmPC, and is also only applicable for products that are approved in the specific age group. This text is acceptable to the Rapporteur.

"*Paediatric population*

A single study of pethidine pharmacokinetics[1] was conducted in 21 infant patients who received a single 1mg/kg dose following surgery or during mechanical ventilation. V_c, V_{ss} and $t_{1/2}$ was shown to vary greatly between infant subjects, but were not demonstrated to correlate with age, gestational age, postconceptional age, weight or body surface area. Clearance was demonstrated to correlate with age, gestational age, postconceptional age, weight and body surface area. Median elimination half-life was demonstrated to be 10.7 hours (range 3.3. to 59.4 hours), median clearance was 8.0 ml/kg/min (range 1.8 to 34.9 ml/kg/min), median volume of the central compartment 2.4 L/kg (range 0.5 to 4.8 L/kg) and median steady-state volume of distribution was 7.2 L/kg (range 3.3 to 11.0 L/kg).

[1] Pokela ML, Olkkola KT, Koivisto M, Ryhanen P. Pharmacokinetics and pharmacodynamics of intravenous meperidine in neonates and infants. Clin Pharmacol Ther 1992;52(4):342-9"

[1] *The recommendation from section V can be copied in this section*.

III. INTRODUCTION

Sanofi-Aventis *recherche et developpement*, Chilly-Mazarin, France (henceforth referred to as Sanofi) did not submit any new completed paediatric studies for pethidine, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

A lengthy (102 pages) critical expert overview prepared by Dr. Carsten Spannhuth has been provided.

The MAH stated that the submitted safety data does not influence the benefit risk for pethidine.

The MAH propose to further revise the pethidine labelling document in order to update paediatric information (however see conclusion above).

IV. SCIENTIFIC DISCUSSION

Pethidine (INN) or meperidine (USAN) is a synthetic opioid analgesic of the phenylpiperidine class. Synthesized in 1939 as a potential anticholinergic agent by the German chemist Otto Eislib, its analgesic properties were first recognised by Otto Schaumann while working for IG Farben, Germany.

Pethidine is indicated for treatment of moderate to severe pain, and is delivered as a hydrochloride salt in tablets, as a syrup, or by intramuscular, subcutaneous or intravenous injection. For much of the 20th century, pethidine was the opioid of choice for many physicians; in 1975 60% of doctors prescribed it for acute pain and 22% for chronic severe pain. Compared with morphine, pethidine was thought to be safer, carry a lower risk of addiction and to be superior in treating the pain associated with biliary spasm or renal colic due to its putative anticholinergic effects. It was later discovered that it carried an at least equal risk of addiction, possessed no advantageous effects on biliary spasm or renal colic compared to other opioids and that, due to its toxic metabolite, norpethidine, it was more toxic than other opioids, especially during long-term use. It was also discovered that the norpethidine metabolite had serotonergic effects which means that pethidine could, unlike most opioids, cause serotonin syndrome.

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

According to the Q&A on paediatric regulation: “A medicinal product is authorised for paediatric use in the context of Article 45/46 if there is either an indication in children (0 to 17 years inclusive) in 4.1, or dosing information for children in 4.2 of the SmPC.”

The statement concerning paediatric population in the current Company [Sanofi] Core Data Sheet version 1 dated 12 January 2010, section 3. Dosage and administration, 3.2 Special populations - Children is the following: “Safety and effectiveness of pethidine in paediatric patients have not been established.”

There is no specific paediatric formulation; the following formulations are available:

- Solution for injection (each mL containing 50 mg of pethidine active ingredient)
- Oral drops (each mL containing 50 mg of pethidine active ingredient)
- Tablets of 50 mg and 100 mg of pethidine active ingredient
- Suppositories of 100 mg of pethidine active ingredient
- Syrup of 50 mg/5 ml of pethidine active ingredient

IV.2 Non-clinical aspects

1. Introduction

No non-clinical safety study has been performed by Sanofi in juvenile animals with pethidine. A literature review was performed in Embase and Medline databases to 13 February 2014 using the following search terms (as thesaurus “Emtree” terms): 'pethidine'/exp AND [animals]/lim AND

'juvenile animal'/exp AND ('side effect'/exp OR 'adverse drug reaction'/exp OR 'drug toxicity'/exp). The review of the available data did not provide any non-clinical safety information relevant to the paediatric use of pethidine**.**

Rapporteur's comment – given the vast clinical experience with pethidine the non-relevance of pre-clinical data from the literature is to be expected.

2. Non clinical studies

Rapporteur's comment – the same comment applies as above.

IV.3 Clinical aspects

1. Introduction

Rapporteur's comment – the clinical overview provides a review of the published literature on studies of pethidine in children which includes a total of 56 studies, categorised below and dating from 1970 to 2012. The studies are reviewed in well written abstracts on pages 22 to 55 of the overview.

The work compiling the review is acknowledged and the interested reader is referred to Table 1 of the MAH's overview (pages 17 to 21). However, in the Rapporteur's understanding the purpose of worksharing exercises such as the present one is to examine studies which have neither been published nor regulatoraly reviewed with the primary aim of establishing whether there are any clinical safety elements relating to the substance which may have been missed through non-review.

Overview of literature references by therapeutic intervention

Therapeutic intervention	Number of studies
Tonsillectomy	12
Ophthalmic surgery	14
Abdominal surgery	4
Other surgery	7
Other pain	3
Sedation [for medical procedures]	15
Tetralogy of Fallot	1

2. Clinical studies

Rapporteur's comment – there are no studies sponsored by the MAH in paediatric populations.

MAH's Safety Data base

Unsolicited cases received from healthcare professionals or consumers, and solicited serious cases involving paediatric patients are presented in the overview.

The Medical Dictionary for Regulatory Activities (MedDRA), version 16.1, was used for coding the solicited AEs and the Adverse Drug Reactions (ADR) captured in the Sanofi global pharmacovigilance database.

The results are presented by age-group classified as follows:

- Neonates: [0–27 days], or patients reported as neonates

- Infants: [28 days to 23 months], or patients reported as infants
- Children: [24 months to 11 years], or patients reported as children
- Adolescents: [12–17 years[, or patients reported as adolescents

A total of 105 unsolicited cases including 94 medically-confirmed (corresponding to 191 reactions) and 11 non-medically confirmed cases (corresponding to 36 reactions), were recorded and are tabulated below.

SOC		Age-group				Total
		[0 - 27 days]	[28 days - 23 months]	[24 months - 11 years]	[12 - 18 years[	
Cardiac disorders	reactions		2	3	7	**12**
	cases		2	2	5	**9**
Eye disorders	reactions			1		**1**
	cases			1		**1**
Gastrointestinal disorders	reactions				1	**1**
	cases				1	**1**
General disorders and administration site conditions	reactions	1	2	14	15	**32**
	cases	1	2	12	14	**29**
Immune system disorders	reactions				3	**3**
	cases				3	**3**
Injury, poisoning and procedural complications	reactions	2	2	5		**9**
	cases	2	2	3		**7**
Investigations	reactions			1	5	**6**
	cases			1	5	**6**

Musculoskeletal and connective tissue disorders	reactions	1	2	2	2	7
	cases	1	2	1	2	6
Nervous system disorders	reactions	7	7	10	9	33
	cases	4	4	8	6	22
Psychiatric disorders	reactions			3	5	8
	cases			2	5	7
Renal and urinary disorders	reactions	1				1
	cases	1				1
Respiratory, thoracic and mediastinal disorders	reactions	3	1	13	8	25
	cases	2	1	12	7	22
Skin and subcutaneous tissue disorders	reactions		2	17	26	45
	cases		2	14	14	30
Surgical and medical procedures	reactions		1	1	1	3
	cases		1	1	1	3
Vascular disorders	reactions	1		1	3	5
	cases	1		1	3	5
Total reactions		**16**	**19**	**71**	**85**	**191**
Total cases		**6**	**11**	**40**	**37**	**94**

One solicited case was retrieved from the search and was provided from the German documentation centre for severe skin reactions. The case involved a 17-year-old female patient with a medical history of chronic myeloid leukaemia who was hospitalised for planned bone marrow transplantation. Her co-medications included metamizole intravenously due to pain and fever, furosemide, pethidine IV, and teicoplanin. Stevens-Johnson syndrome with a fatal outcome and 6 reactions were coded (corneal lesion, mouth ulceration, multi-organ failure, blister, rash and Stevens-Johnson syndrome).

Rapporteur's comment – the MAH comments on the safety database in considerable detail (pages 82 - 94). The events appear to be due to the complications of surgery, to therapeutic errors, and to the known unwanted effects of opiates, for example respiratory depression. There were seven fatal events (six medically confirmed) which appear to share the same pattern of causation with the non-fatal events.

3. Discussion on clinical aspects and conclusion

The most important point in regard to the present paediatric work-sharing procedure is regulatory. The sole respondent to the request for data is Sanofi which company has not conducted any studies of pethidine in non-adult populations and has product information which carries a discouragement to use in children, in the form of a statement that safety and efficacy in children have not been established. Therefore, there are no new data to suggest that regulatory action might be required.

Sanofi's helpful analysis of the literature largely confirms that pethidine is an effective opiate analgesic and a sedative, although apparently it has a formal therapeutic indication for sedation in the EU only in Hungary.

Analysis of the Sanofi clinical safety data base confirms (through reports of AEs) that Sanofi's brand of pethidine is used in children but cannot provide meaningful data on the frequency of such events due

to lack of knowledge of the market share of total use of pethidine in children. Equally, such data are impossible to generate from the literature cited in the company's clinical overview. The qualitative data resemble what might be expected of a powerful opiate.

Unlike in adults where an unknown but non-negligible proportion of pethidine use is for the treatment of chronic pain the predominant use in children is during and after surgery and the adverse event profile reflects the hazards of surgery probably in greater proportion than the hazards of use of an opiate analgesic. Those events which fit the known adverse event profile of pethidine are similar to those in adults. However, the Sanofi safety database is too small and is not designed to determine whether there might be any child specific safety problems.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➢ Overall conclusion

Only one company has provided information relative to the paediatric use of pethidine but has not conducted any company sponsored studies. Therefore, there are no new data forthcoming in relation to the efficacy or safety profile for use in children. However, as pethidine has been in common use for over half a centaury it is reasonable to assume that its efficacy and safety profile is well understood in adults and children.

➢ Recommendation

See below.

VI. ASSESSMENT OF RESPONSE TO QUESTIONS

AGENCY QUESTION / REQUEST FOR INFORMATION ITEM NO. 1:

The conclusion of the Clinical Overview is to update the product information in relation to paediatric use, however there is no relevant information as to how the product information is to be updated. Please supply the relevant information and a brief explanation/justification.

Sanofi response:

A publication[2] showed that for term neonates less than 5 days, plasma clearance was lower (7.2 mL/min/kg) than in children between 4 and 8 years (10.4 mL/min/kg) (2). In neonates and infants between 3 weeks and 5 months, a mean clearance close to the one observed in children was observed (9.7 mL/min/kg versus 10.4 mL/min/kg, respectively) but with a larger inter-subject variability (4.1 - 20.5 mL/min/kg versus 8.4 – 13.6 mL/min/kg).

The company made a search in the Sanofi global pharmacovigilance database, in the literature, and in the medical textbooks (Martindale and Meyler's) in order to assess the clinical impact of the pharmacokinetic data. The details of this search are outlined in the Clinical Overview ([Appendix 1: Clinical Overview: Pethidine safety in neonates and infants]) dated 24 October 2014. The conclusion is that the weighted cumulative evidence is insufficient to demonstrate a clinical impact of the

[2] Pokela ML, Olkkola KT, Koivisto M, Ryhanen P. Pharmacokinetics and pharmacodynamics of intravenous meperidine in neonates and infants. Clin Pharmacol Ther 1992;52(4):342-9

pharmacokinetic data in neonates and infants less than 12 months. However, the company will monitor this topic.

Due to divergent opinions among EU Member States (MS) it is not possible to achieve harmonised product information (SmPC/PIL) in the current work sharing procedure. Those MS where paediatric use of pethidine is not contraindicated or where there is not a warning/recommendation against such use might consider allowing the addition of a statement such as that proposed by Sanofi by way of national variation.

“Pethidine has a slower elimination rate and a larger inter-subject variability in neonates and young infants compared to older children and adults, which may lead to dose related reactions such as respiratory depression. If pethidine use is contemplated in neonates or young infants (up to 12 months), any potential benefits of the drug need to be weighed against the relative risk to the patient.”

VII. FINAL RAPPORTEUR’S OVERALL CONCLUSION AND RECOMMENDATION

Overall conclusion

Please see page 4 of this report. Amendments may be made to sections 4.4 and 5.2 of the SmPC as described.

Recommendation

As above

VIII. LIST OF MEDICINCAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Sanofi is the sole MAH to have provided information.