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

Pentamidine

DK/W/020/pdWS/001

Rapporteur:	Denmark
Finalisation procedure (day 120):	April 22, 2013
Date of finalisation of PAR	May 17, 2013

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section VII
INN (or common name) of the active substance(s):	Pentamidine
MAH (s):	Sanofi Avensis
Pharmaco-therapeutic group (ATC Code):	P01CX01
Pharmaceutical form(s) and strength(s):	Powder for solution for injection 200 mg and 300 mg Powder for nebuliser solution 300 mg

I. EXECUTIVE SUMMARY

No SmPC and PL changes are proposed.

Summary of outcome

☒ No change

☐ Change

☐ New study data: <section(s) xxxx, xxxx>

☐ New safety information: <section(s) xxxx, xxxx>

☐ Paediatric information clarified: <section(s) xxxx, xxxx>

☐ New indication: <section(s) xxxx, xxxx>

II. RECOMMENDATION[1]

The recommendations as outlined in this assessment report are generally not considered within the scope of the article 45 paediatric worksharing procedure. The recommendations should not be limited to use in children, as these also apply for adults. The company has agreed to initiate variations to address the recommendations in order to achieve a harmonized position in EU.

The company intends to ask each European country to update their local labeling according to the following recommendations:
The local PIs should clearly indicate that IV treatment is the preferred route of administration for the treatment of PCP.
The inhalation route is not recommended for the treatment of mild PCP and should be removed from all PIs, where this recommendation is still included. The IV route is considered the preferred route of administration for the treatment of PCP. The inhalation route should be used for prophylaxis of PCP only.
This is accepted by the Rapporteur.

The company is also recommended to discuss in the next submitted labelling variation the current state of the art in terms of mode of administration (IM or IV) for the other authorised indications: trypanosomiasis and leishmaniasis.

III. INTRODUCTION

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

In accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use, Sanofi-Aventis has submitted relevant paediatric data concerning pentamidine for assessment.

Pentamidine is an “old” drug which has been used for more than 40 years in the treatment of the early stages of human African trypanosomiasis (HAT), also known as sleeping sickness, in some forms of leishmaniasis, and in the treatment and prophylaxis of pneumocystis pneumonia (PCP). The first marketing authorization (MA) was received in the United Kingdom (UK) on 15-Jun-1988, and pentamidine isetionate is currently approved and marketed in about 20 countries

Only few historical data exists regarding the use of pentamidine in children. The currently available SPCs across EU have some minor differences regarding indications and dosage recommendations, but overall most SPC does not discern between use in children and adults.

The following dosages are recommended for adults, children and infants:

• In the treatment of **pneumocystis pneumonia**, pentamidine isetionate 4 mg/kg is commonly given once daily for 14 days or longer, by slow IV infusion (or by IM injection).
• The safety and efficacy of pentamidine isetionate given by inhalation to prevent pneumocystis pneumonia in children have not been established. Therefore, the paediatric practice follows the recommendations that have been extrapolated from adult studies and the HIV literature. In HIV-positive adult patients, pentamidine isetionate is usually given trough a nebulizer in a dose of 300 mg once every 4 weeks.

• In *visceral* **leishmaniasis** that has not responded to antimonials, pentamidine isetionate is given at a dose of 3-4 mg/kg, preferably by IM injection, on alternate days to a maximum of 10 injections; if necessary the course can be repeated. In *cutaneous* **leishmaniasis** due to *Leishmania aethiopica* or *Leishmania guyanensis,* pentamidine isetionate is given at a dose of 3-4 mg/kg, preferably by IM injection, once or twice weekly, until the condition resolves, i.e. generally for 3-4 injections.

• In the treatment of *early* **human African trypanosomiasis** (HAT) due to *Trypanosoma brucei gambiense,* pentamidine isetionate was usually given at a dose of 4 mg/kg on alternate days, but it is nowadays preferentially given at a dose of 4 mg/kg daily by IM injection or IV infusion to a total of 7 to 10 doses. Pentamidine is not effective in the late stage of trypanosomiasis with central nervous system (CNS) involvement.

In the absence of new clinical data, and very scarce paediatric data, the submitted data from the MAH primarily consists of:

1) A Critical Expert Overview, which is primarily based on previously submitted expert reports dated between 1987 and 1989 on the intravenous or inhalational use of pentamidine and an updated literature search
2) Internal pharmovigilance data.

There is no non-clinical information relevant to the paediatric use of pentamidine.

The MAH states that no new safety concerns have been identified regarding the use of pentamidine in children in terms safety and that the benefit/ risk ratio of pentamidine solution for injection and nebuliser solution remains favourable for use in accordance with the prescribing information in the indications currently approved.

As for the Summary of Product Characteristics (SPC), although not in the scope of the Article 45 procedure, the MAH propose to harmonize the SPCs in regard to the dosing interval for the trypanosomiasis indication, to include in all SPCs the option of once daily dosing. The wording in the dosage section would then read “4 mg/kg body weight once daily or every other day up to a total number of 7-10 doses”.

Summary of pediatric information in SPC across EU
There are several differences in the currently approved EU SPCs.

IV. SCIENTIFIC DISCUSSION

IV.1 PRELIMINARY SCIENTIFIC DISCUSSION

IV.1.1 Non-clinical aspects

Introduction

5.1 PHARMACODYNAMICS
Pentamidine (ATC code P01CX01), an aromatic diamidine derivative, is an antiprotozoal agent which is also active against Pneumocystis which belongs to the fungal kingdom. Its mechanism of action is not fully understood and possibly includes interference with protozoal DNA and folate transformation, and by inhibition of group I intron ribozymes in Pneumocystis.

Pentamidine has been given as the mesilate salt and is now available in most countries as the isetionate salt. Pentamidine isetionate contains 1 g of base per 1.74 g of salt, while pentamidine methanesulfonate contains 1 g of base per 1.56 g of salt.

Pentamidine isetionate is not absorbed after oral administration and is given by deep Intramuscular (IM) injection or by slow intravenous (IV) infusion over at least 60 minutes. Direct IV injection (bolus) should be avoided. Pentamidine isetionate is also given by inhalation through a nebulizer to prevent PCP.

Paediatric information:
The dosage of pentamidine is expressed as mg per kg body weight, and the indications for use and doses of pentamidine isetionate administered by IM injection or IV infusion in infants and children are generally considered to be the same as those for adults.

5.2 PHARMACOKINETICS

The renal clearance constitutes only a small fraction of plasma clearance of pentamidine and indicates that metabolism is a major route of elimination.

After parenteral administration of 4 mg/kg of pentamidine diisethionate (isetionate):
- In patients with normal renal function: the peak blood concentration observed respectively at the end of the infusion and less than one hour after IM injection is approximately 500 ng/mL after IV administration and 200 ng/mL after IM administration.
The elimination half-life is longer after IM administration (about 9.4 hours) than after IV administration (about 6.2 hours). After multiple intravenous doses the half-life is 21.5 days.

The apparent volume of distribution at steady state is three times higher after IV infusion (approximately 2700 L) than after IM injection (approximately 820 L).
- In patients with renal impairment, due to the decrease in body clearance of the product, there is an accumulation with increased half-life Cmin and volume of distribution.
- After aerosol administration of 4 mg/kg of pentamidine isetionate, the kinetic parameters of pentamidine are significantly different from those observed following parenteral administration:
- A peak plasma concentration of14 ng/mL (±12) is observed by the end of the first hour after aerosol representing approximately 10% and 5% of concentrations observed after IM and IV administration, respectively.
- After repeated treatment every day for 21 days, no marked plasma accumulation was reported, with peak is 20.2 ng/mL (±21.4) and Tmax reached around the fifth day.
- Concentration in the bronchial alveolar lavage (BAL) fluid: After aerosol administration, the concentrations found in the BAL are higher than those observed.

IV.1.2 Non clinical study(ies)

No new non clinical studies were submitted

IV.1.3 Clinical aspects

Introduction

In the submitted review, a brief review of the three diseases for which pentamidine is used are given together with a summary of more recent clinical reports published during the last 10 years. In the following this review together with a brief summary of the submitted reviews of recent essential studies are given:.

PCP

Pneumocystis jiroveci (previously known as *Pneumocystis carinii*) is an unusual fungal opportunistic organism, which causes a severe and often fatal pneumonia in immunocompromised individuals. Until 1980 Pneumocystis pneumonia (PCP) was uncommon and primarily observed in association with syndromes of immunodeficiency or intensive immunosuppression, in particular cancer chemotherapy. With the HIV-1 pandemic, however, PCP emerged as the most common AIDS defining disease in industrialized countries. Before systematic PCP prophylaxis was introduced, PCP was observed as the AIDS defining event in 60% of HIV-1 infected patients and it was estimated that up to 80% of patients with CD4 counts less than 200 would eventually develop PCP. Following the introduction of primary and secondary PCP prophylaxis in the early nineties a decline in the incidence of AIDS related PCP was observed, which further markedly declined after the introduction of highly active antiretroviral therapy in the mid-nineties. Nevertheless, PCP continues to be a common disease with a substantial morbidity and mortality.

The highest incidence of PCP in HIV-infected children is in the first year of life, with cases peaking at age 3-6 months.

Trimethoprim- Sulfamethoxazole (TMP-SMX) combination is the drug of choice for the treatment and prevention of PCP.

For many years, pentamidine was used as the primary second choice in patients unresponsive to, or intolerant of TMP-SMX for treatment of PCP (by intravenous treatment, also earlier by

inhalation, but this route has largely been abandoned due to inferior efficacy) and for the prevention of PCP by inhalation in high risk children and adults.

• For treatment of PCP:

In two randomized clinical trials (RCTs) of HIV-associated PCP, TMP-SMX and pentamidine were equally effective [1, 2]. However, interpretation of these trials remains limited by a high rate of treatment switches due to toxicity or treatment failure and a limited sample size. In a small non-crossover RCT, treatment with TMP-SMX was associated with fewer adverse events and improved survival [3]. Subsequent trials have demonstrated comparable efficacy of oral TMP-SMX, clindamycin/primaquine and trimethoprim/dapsone, but patients with severe PCP were excluded. Use of primaquine, dapsone and trimethoprim may be restricted, because they can only be administered orally. Thus, intravenous pentamidine has been recommended as the main alternative to TMP-SMX for moderate to severe PCP in spite of its toxicity.

- The overall recommendations for treatment of PCP have been summarized by CDC in the Guidelines (2009 updated version) for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children [4]:

Pentamidine isetionate IV once daily is recommended for patients who cannot tolerate TMP-SMX or who demonstrate clinical treatment failure after 5-7 days of TMP-SMX therapy (Strength of the recommendation: A; Quality of evidence: I). No evidence exists for synergistic or additive effects on efficacy of these agents; therefore, because of potential increased toxicity, their combined use is not recommended (DIII). Among patients with clinical improvement after 7-10 days of IV therapy with pentamidine, an oral regimen (e.g., atovaquone or TMP/dapsone) might be considered to complete a 21-day course (BIII).

• For the prophylaxis of PCP

Paediatric recommendations have been extrapolated from adult studies and the HIV literature, and thus some discrepancies exist across guidelines.

With regard to aerolized pentamidine in prophylaxis of PCP, five trials including 1,130 patients were conducted. Very few children (two identified) were reported in these initial trials, and only some case reports and case series in this setting were identified in the literature.

- WHO recommendations for the prophylaxis of PCP: Pentamidine by inhalation of nebulized solution, *adult,* 300 mg as a single dose once every 4 weeks, *child*, 4 mg/kg as a single dose once every 4 weeks. Pentamidine by slow IV infusion, *adult and child*, 4 mg/kg once every 4 weeks.
- Current CDC recommendations: Aerosolized pentamidine is recommended for children who cannot take TMP-SMX, atovaquone, or dapsone and are old enough to use nebulization with a Respirgard II(r) nebulizer (Marquest, Englewood, CO) (BI). The dosage for all ages is 300 mg once a month.

Intravenous prophylaxis: Although IV pentamidine is not recommended for prophylaxis (EIII), the administration of aerolized pentamidine requires specialized equipment and personnel that may not be available at all centers, and there is the concern that younger children may not receive an adequate amount of the drug due to difficulties in delivery.
Therefore, many institutions utilize IV pentamidine as prophylaxis even though there are few published data to support its efficacy in the paediatric population.

- With regard to discontinuation of the prophylaxis, the CDC considers that available data support the expectation for very low risk for PCP after prophylaxis is discontinued in children who have achieved immune reconstitution. In most patients, secondary prophylaxis can be discontinued using the same criteria as for

Treatment of Pneumocystis Pneumonia
The MAH clinical review identified one systematic review on treatment of PCP was identified in the literature. No data on age were specified in this review.

• **Benfield T, et al. 2008** [5]
Limited clinical data exist to guide the choice of second-line salvage treatment for AIDS associated PCP. Thus, the authors conducted a systematic search of Medline for all randomized and observational studies of PCP treatment published up to August 2007 and included individual treatment data of AIDS-associated PCP from a tri-centre study (Copenhagen, London, Milan).

Pooled estimates of reported outcome of second-line treatment were calculated using averaged odds ratios (ORs). Second-line salvage treatment was defined as the regimen given after a change of the primary drug regimen on the grounds of suspected treatment failure and occurring after at least 5 days of therapy for AIDS-associated PCP. Thus were excluded all the studies in which treatment was switched after less than 5 days of therapy, studies describing switches attributable to toxicity, and studies of non-HIV-infected patients.

Twenty-nine studies with sufficient detail of second-line treatment and outcome, including 28 studies from the literature and data from 82 individual cases from the tri-centre study, yielded a total of 468 PCP second-line treatment episodes. Forty-five patients initially received TMP-SMX; 28 switched to IV pentamidine and 17 switched to clindamycin-primaquine. Fifteen patients initially received IV pentamidine; 5 switched to clindamycin-primaquine and 10 switched to TMP-SMX. Eight patients initially received clindamycin-primaquine; 5 switched to IV pentamidine and 3 switched to IV pentamidine. Fourteen patients initially received inhaled pentamidine; 11 switched to TMP-SMX and 3 switched to IV pentamidine. Response rates to second-line treatment were 68% for TMP-SMX, 73% for clindamycinprimaquine (OR for response = 2.1 [95% CI, 1.1 to 3.2] and 2.7 [95% CI, 1.3 to 4.0], respectively), whereas they were 44% for intravenous pentamidine (OR = 0.8 [95% CI, 0.6 to 1.0]).

Prophylaxis of Pneumocystis Pneumonia
One retrospective study was identified on pentamidine IV in the prophylaxis of pneumocystis pneumonia in paediatric oncology patients.

• **Kim SY, et al. 2008 [6]**
The use of TMP-SMZ prophylaxis virtually eliminates the risk of PCP; however, many patients cannot tolerate TMP-SMX. This retrospective analysis was performed to determine the PCP breakthrough rate in paediatric oncology patients receiving IV pentamidine as second line PCP prophylaxis from 2001 to 2006. The diagnosis, age and bone marrow transplant (BMT) status were determined (age unspecified). A subset of patients had review of their records to determine the justification for discontinuing TMP-SMX. Children who developed symptoms of pneumonia with a clinical suspicion of PCP underwent bronchoscopy, allowing for identification of *Pneumocystis*.

A total of 232 patients received 1,706 doses of IV pentamidine and no toxicities were identified. The main reasons for discontinuing TMP-SMX were bone marrow suppression and drug allergy.

Three children developed PCP, equating to a breakthrough rate of 1.3%. Two of these children had undergone BMT (1.9% breakthrough rate) and both were under 2 years of the age (6.5% breakthrough rate). The authors concluded that the use of IV pentamidine as PCP prophylaxis in children results in a breakthrough rate of 1.3%. TMP-SMX is the first choice for PCP prophylaxis. However, when necessary, the use of IV pentamidine has an acceptably low failure rate, even in high-risk BMT patients. Other options should be considered for children less than 2 years of age.

Assessor's comment

Treatment of PCP

This assessor was author of the cited meta-analysis above - in a subsequent paper we did a more detailed analysis of the tri-centre study (DK, UK, Italy: Clinical efficacy of first- and second-line treatments for HIV-associated Pneumocystis jirovecii pneumonia: a tri-centre cohort study. JAC, 2009, 64(6):1282-90. Helweg-Larsen J et al [7]) In our cohort none of the included patients were children. It must be emphasized that the vast majority of clinical studies included in the meta-analysis only included adults. Efficacy and safety data for pentamidine therefore has to be extrapolated from adults. In our study and previously published studies, overall, iv pentamidine appeared more toxic compared to TMP-SMX and clindamycine/primaquine. However, iv pentamidine continues to be an important secondary treatment option for PCP in patients unable to tolerate other alternative treatment options for PCP, particularly when oral treatment is not safe (e.g primaquine is only available orally and contraindicated in G6PD deficiency).
It should be noted that during our/ my review of the efficacy data as well of our own historical data it was evident that inhalational pentamidine performed overall poorly for HIV-associated PCP, many patients failed this treatment and had to be switched to intravenous treatment. This is supported by a small RCT in which failure with inhaled pentamidine was higher compared to iv pentamidine[8].

Inhalational pentamidine cannot be recommended for treatment of PCP, regardless of severity, at presentation it is difficult in clinical practice to identify patients with "mild" PCP, and a substantial fraction of patients with PCP will deteriorate during treatment. Therefore inhaled pentamidine is obsolete and should not be used for treatment. In contrast, pentamidine inhalation is efficient and well-tolerated for the prophylaxis of PCP. Current SPCs from Germany, Ireland and UK continues to recommend inhaled pentamidine for treatment of (mild) PCP- this needs to be changed.

Prophylaxis of PCP

The MAH review failed to cite another important study examining intravenous prophylaxis: Pneumocystis pneumonia in children receiving chemotherapy. Prasad P et al [9]. In this study, PCP prophylaxis in all children up to 18 years of age undergoing cancer chemotherapy at the Vanderbilt University Medical Center between 2003 and 2005 were retrospectively reviewed. Four children were diagnosed with PCP over 24 months. Two of 12 children on intravenous pentamidine, 1 of 143 on TMP-SMZ and 1 of 36 on dapsone for PCP prophylaxis developed PCP. Based on this study intravenous pentamidine prophylaxis may not be as effective as previously considered and should be used with caution.

As regards efficacy of prophylactic intravenous pentamidine in children, this treatment has been used off-label in several centres, particularly in children with hematological malignancies or BMT. Although this treatment may be an option in certain cases,-clinical data are not convincing and there is insufficient basis to provide support for a formal indication for the use of intravenous prophylaxis in children.

Leishmaniasis

Leishmaniasis is caused by the parasitic protozoa, *Leishmania,* and is usually categorized as visceral, cutaneous, or mucocutaneous. It may manifest as a self-limiting localized skin lesion but can progress from this to mucosal involvement, to disseminated progressive disease (in the cutaneous form) or, without treatment, to a fatal disease (in the visceral form). With some exceptions, human beings are the incidental hosts of infection, and mammals, such as rodents and canids, are the reservoir hosts. The parasites are transmitted by sand flies.

Visceral leishmaniasis (kala-azar) is caused by *Leishmania donovani* and *L. infantum* (Old World) and by *L chagasi* (New World). Cutaneous leishmaniasis comprises the Old World variety caused by *L. tropica*, *L. major*, *L. infantum*, or *L. aethiopica*, and the New World variety caused by *L. braziliensis*, *L. mexicana* and *L. guyanensis*. Mucocutaneous leishmaniasis is caused by *L. braziliensis*; in this form of the disease, the primary lesions do not heal and spread to the mucosa may occur. Lastly, diffuse cutaneous leishmaniasis usually occurs following infection with *L. amazonensis*, *L. aethiopica* or *L. Mexicana.* Children are the primary victims of leishmaniasis. The main age groups affected by the disease are generally children under 5 years of age for Old World visceral leishmaniasis and children under 10 years of age for New World visceral leishmaniasis, whereas cutaneous leishmaniasis frequently occurs in older children and young adults.

The clinical manifestations of childhood **visceral leishmaniasis** are generally the same as in the adults. Prolonged fever with anorexia and loss of appetite are the major presenting features, followed by enlargement of the spleen and liver.
Cutaneous leishmaniasis can present a variety of clinical features and courses, depending on virulence factors and host immune response. In general, the lesions are confined to a given area of the skin (localized cutaneous leishmaniasis), but parasites can diffuse to other skin areas (diffuse cutaneous leishmaniasis) or to facial mucosa (mucocutaneous leishmaniasis) .

Current recommendations and guidelines for the treatment of leishmaniasis in its different clinical forms have been published including those from the WHO, MSF, the CDC and the French Societé de Pathologie Exotique.

The various species of leishmaniasis respond differently to drugs.

As recommended by the WHO Model Formulary 2008, pentamidine is indicated in the treatment of different forms of leishmaniasis. Dosage regimens by indication are similar for adults and children, and they are as follows:

• **Visceral leishmaniasis** (unresponsive to, or intolerant of, antimonial compounds): pentamidine by slow IM or IV injection or by IV infusion, *adult and child***,** 4 mg/kg 3 times a week for 5-25 weeks or longer, until two consecutive splenic aspirates taken 14 days apart are negative.

• **Cutaneous leishmaniasis** (infections caused by *L. aethiopica, L. guyanensis*): pentamidine by deep IM or IV injection or by IV infusion, *adult and child***,** 3-4 mg/kg once or twice a week until the lesion is no longer visible; relapse is unusual.

Diffuse cutaneous leishmaniasis (infections caused by *L. aethiopica*): pentamidine by deep IM injection or by IV infusion, *adult and child,* 3-4 mg/kg once a week, continued for at least 4

months after parasites are no longer detectable in slit-skin smears; relapse are frequent during the first few months until immunity is established.

• **Mucocutaneous leishmaniasis** (unresponsive to antimonial compounds): pentamidine by deep IM injection or by IV infusion, *adult and child***,** 4 mg/kg 3 times a week for 5- 25 weeks or longer, until lesion is no longer visible. With regard to the treatment of the New World cutaneous leishmaniasis, a recent systematic review and meta-analysis showed that the cure rate with pentamidine is similar to that obtained with pentavalent antimonials . Pentamidine is recommended as first-line treatment for cutaneous leishmaniasis caused by *L. guyanensis* in French Guyana by the French "Societé de Pathologie Exotique". The same recommendation is provided by the CDC, with a paediatric dose of 2 to 3 mg/kg IM or IV once a day or every other day for 4 to 7 doses.

In the MSF Guidance for prescribing (January 2010), pentamidine is among the drugs recommended as second line in the event of non-response to pentavalent antimonials in the visceral, cutaneous and mucocutaneous forms of leishmaniasis: Pentamidine slow deep IM injection (with the patient supine), *children and adults*, 4 mg/kg injection on alternate days for a total treatment duration of 5 to 25 weeks, until no parasites are detected on microscopy (for visceral leishmaniasis), 2 negative biopsy-aspirates at an interval of 14 days. In conclusion, children are particularly affected by leishmaniasis. Among the drugs currently available, pentamidine is the first option for cutaneous leismaniasis caused by *L. guyanensis* and it is recommended in the visceral form of leishmaniasis in patients unresponsive to, or intolerant of, antimonials. The dose most commonly used is 3-4 mg/kg per administration, the dose interval and duration of treatment depending on the clinical form of the leishmaniasis

Visceral leishmaniasis
One retrospective study and one recent meta-analysis were identified regarding pentamidine in visceral leishmaniasis.

• **Minodier P, et al. 1998**[10]
In this retrospective study the characteristics of paediatric visceral leishmaniasis in southern France were described and a new scheme of therapy was evaluated. Hospital records of 59 children with visceral leishmaniasis were reviewed. The period of the study was from 1981 to 1997. All children but one lived or had previously dwelled in the south of France. None was coinfected with human immunodeficiency virus or known to be immunocompromised. The mean age was 31 months; 10 children were younger than 1 year when admitted to the hospital. All patients were initially treated with meglumine antimonate. Among 59 children, 33 (55.9%) were treated with meglumine antimonate and pentamidine (n=19) or with meglumine antimonate and pentamidine isethionate (n=14). These patients received antimony for 15 days followed by diamidine (12 injections). The mean doses of pentamidine and pentamidine isethionate were 2.4 and 3.9 mg/kg/injection, respectively. Seventeen (28.8%) patients received only meglumine antimonate (17 mg antimony/kg/day, incremental increases in dosage), for 1 month as recommended by WHO. Eight (13.5%) children received meglumine antimonate followed by liposomal amphotericin B (mean dose, 3.3 mg/kg/day for 10 days). One additional patient (1.7%) was treated with three courses of meglumine antimonate and one course of pentamidine, then with 3 mg/kg/day of liposomal amphotericin B for 10 days. Twenty-six (44%) patients receiving the drug experienced at least one adverse event during treatment. Treatment failure occurred in six children (10%), who were subsequently cured with liposomal amphotericin B. Three additional children were treated with liposomal amphotericin B.All the children were finally cured and no death was observed. The authors concluded that liposomal amphotericin B is effective therapy for visceral leishmaniasis in children.

• **Olliaro PL, et al. Systematic review and meta-analysis. 2005 [11]**
The state of Bihar in India carries the largest share of the world's burden of antimony-resistant visceral leishmaniasis. Therefore the authors of this review analysed clinical studies done in Bihar with different treatments between 1980 and 2004. Overall, 53 studies were included (all but one published), of which 15 were comparative (randomised, quasi-randomised, or non-randomised), 23 dose-finding, and 15 non-comparative. Data from comparative studies were pooled when appropriate for meta-analysis. Regimens with pentamidine (isethionate or methanosulfonate) were tested in six published and one unpublished trial, all done between the 1980s and 1990s. No recent studies were available. With one exception, in all studies the drug was administered at 4 mg/kg per day for a variable number of infusions.
Overall, these studies enrolled 7,263 patients in 123 treatment arms. Adequacy of methods used to do the studies and report on them varied. Unresponsiveness to antimony has developed steadily in the past to such an extent (cure rates to 36-69% only) that antimony must now be replaced, despite attempts to stop its progression by increasing dose and duration of therapy. The authors stated that the classic second-line treatments are unsuited in Bihar State: *Regarding pentamidine, efficacy appeared to correlate with the number of infusions, although there has been a general decline from the high cure rates of the early 1980s. The concomitant or sequential addition of antimony did not appear to represent a substantial improvement. Diabetes mellitus was the main safety concern and was reported in 4 to 12% of cases*. Amphotericin B deoxycholate was effective but required hospitalisation for long periods and toxicity was common (e.g. hypokalaemia, nephrotoxicity, myocarditis). Liposomal amphotericin B was very effective and safe but currently unaffordable because of its high price. Miltefosine- the first oral drug for visceral leishmaniasis- is now registered and marketed in India and is effective, but should be used under supervision to prevent misuse. Paromomycin (or aminosidine) is effective and safe,

Cutaneous leishmaniasis
One retrospective study including children and one recent meta-analysis were identified regarding pentamidine in cutaneous leishmaniasis.

• **Lai A Fat EJ, et al. 2002 [12]**
This retrospective study was performed to evaluate the results of treatment with pentamidine mesylate in 235 patients and with pentamidine isethionate in 80 patients suffering from New World cutaneous leishmaniasis. The patients were treated in Surinam between 1979 and December 2000. Of the 315 patients included in the study, 23 were 14 years of age or less. In the small number of patients in whom cultures were performed, *L. guyanensis* was isolated.

In the pentamidine mesylate- and pentamidine isethionate-treated groups, a cure rate (healing without relapse) of nearly 90% was found. Relapses were seen in approximately 10% of patients in both groups. More precisely, in the pentamidine isetionate group, 77 of the 80 patients (96.3%) were healed within 0-4 weeks (mean, 1.91 weeks) after the last injection. Sixty patients were healed with three injections (75%), 12 with four (15%), three with five (3.75%), one with seven (1.25%), and one with 12 (1.25%). The three remaining patients were healed within 6 weeks after the third injection. Treatment with 3-4 injections resulted in 90% healing within 0-4 weeks (mean, 1.86 weeks) after the last injection, and treatment with 3-12 injections resulted in 100% healing within 0-6 weeks (mean, 1.93 weeks) after the last injection. Of the eight (10%) relapses in the pentamidine isetionate-treated group, seven were treated successfully with another course of pentamidine isetionate: four patients with three injections, two with four injections, and one with seven injections. The lesions were cured within 0-4 weeks (mean, 1.33 weeks) after the last injection. The other patient was treated successfully with liquid nitrogen.

Minor side-effects, such as pain at the injection site, bitter taste, and nausea, were seen with both drugs in about 65% of patients. Complaints of the respiratory tract were seen in less than 10% of patients in the pentamidine isethionate-treated group, but were uncommon in the pentamidine mesylate-treated group.
In author's opinion, pentamidine mesylate and isethionate were safe and effective drugs in the treatment of cutaneous leishmaniasis in Surinam.

• Tuon FF, et al. Systematic review and meta-analysis – New World cutaneous leishmaniasis. 2008 [13]
The aim of this systematic review and meta-analysis was to determine the best drug management in the treatment of cutaneous leishmaniasis in Latin America (New World cutaneous leishmaniasis) based on a comprehensive literature search from 1966 to 2006. Articles with adequate data on cure and treatment failure, internal and external validity information, and more than 4 patients in each treatment arm were included.

A total of 54 articles met inclusion criteria and 12 were included in the meta-analysis. Approximately 50% of all patients (1,458 patients) were treated with pentavalent antimonials.Pentamidine was the second most studied drug, employed in 26.6% of cases (759 patients) and used alone at the usual 4 mg/kg daily dosage, followed by paromomycin (352 patients).Pentavalent antimonials such as meglumine and stibogluconate were the most studied drugs, achieving a cure rate of 76.5%. There was no difference in response to pentavalent antimonials according to species (*L. braziliensis*, *L. amazonensis*, and *L. guyanensis*).
Cutaneous leishmaniasis therapy with pentamidine was evaluated not only as a primary treatment option but also in the case of failure of pentavalent antimonial therapy. Pentavalent antimonials (20 mg/kg/20 days) showed worse results than pentamidine (4 mg/kg/7 days) in patients suffering from cutaneous leishmaniasis caused by any *Leishmania* species (77% vs. 87%, $p < 0.05$). This difference was not supported by the meta-analysis, when a direct study of drug efficacy showed similar results (OR, 0.81; 95% CI, 0.64-1.10). In those patients who failed on pentavalent antimonials, pentamidine showed better results. Despite the decreased number of studies, response rates of 87.2% were found, whereas only 63.6% of patients re-treated with pentavalent antimonials showed a favourable outcome ($p < 0.05$).
Other drugs showed variable results, and all demonstrated an inferior response.
The reviewers concluded that although pentavalent antimonials are the drugs of choice in the treatment of cutaneous leishmaniasis, pentamidine showed similar results.

Mucosal leishmaniasis
One recent meta-analysis was identified regarding pentamidine in cutaneous leishmaniasis.

• Amato VS, et al. Systematic review. 2007 [14]
The aim of this systematic review was to determine the best drug management for treatment of mucosal leishmaniasis in Latin America based on the best studies offered by the medical literature.
A total of 22 articles met inclusion criteria, regarding 635 patients. The number of controlled randomised trials was not sufficient to perform a meta-analysis. Stibogluconate achieved a 51% cure rate (76/150 patients), and 88% of patients treated with meglumine antimoniate were cured (121 patients). Pentamidine and amphotericin B were as effective as meglumine. Use of itraconazole and other therapies (pentoxifylline, allopurinol, or interferon-gamma) appeared not well established, and the numbers of patients in some studies were insufficient for statistical analysis.
Regarding pentamidine, in 2 studies from Brazil, a regimen of 4 mg/kg administered on alternate days by the intravenous route to naïve patients with moderate to high-grade lesions (total of 27

patients) was shown to be more effective than stibogluconate and comparable to meglumine, yielding cure rates of 90 to 94%.
The reviewers concluded that meglumine may be the drug of choice in the treatment of mucosal leishmaniasis, as it offers similar cure rates when compared with amphotericin B and pentamidine.

Assessor's comments
Based on the literature review and limited pediatric data, no new efficacy or safety data for the pediatric indication of leishmaniasis have been identified. In the study by Olliaro et al from Bihar, India, a concerning high incidence of diabetes was reported in the range of 4 to 12% of cases. However, it is unclear from this report, whether this was regular diabetes or just intermittent hypoglycemia which is a well-known AE of pentamidine, other studies have not reported such high incidence of diabetes.

In accordance with the current WHO recommendations, pentamidine continues to have an important but restricted role for the treatment of certain forms of leishmaniasis.

Trypanosomiasis

Human African trypanosomiasis (HAT) is caused by the protozoan parasite *Trypanosoma brucei* (*T. brucei*) transmitted by the bites of the tsetse flies. Almost all cases (over 95%) are due to *Trypanosoma brucei gambiense (T b gambiense)*, which is indigenous to west and central Africa, while *T b rhodesiense* causes more acute disease in east and southern Africa. Disease transmission occurs in children and adults during activities such as farming, hunting, fishing, or washing clothes. Prevalence is strongly dependent on control measures, which are often neglected during periods of political instability, thus leading to resurgence. With approximately 12,000 cases of this disabling and fatal disease reported per year, trypanosomiasis belongs to the most neglected tropical diseases.

The course of the disease evolves in two stages. In the first, haemolymphatic stage, the leading signs and symptoms are chronic and intermittent fever, headache, pruritus, lymphadenopathy, and, to a lesser extent, hepatosplenomegaly. In the second stage, sleep disturbances and neuropsychiatric disorders dominate the clinical presentation. HAT is typically fatal if there is no chemotherapeutic intervention.
A three-step approach is used for diagnosis within control programs and for individual patients: screening by means of the card agglutination test for trypanosomiasis/ *T b gambiense* (CATT); parasitological confirmation by the microscopic examination of lymph node aspirate and blood, or both; and staging by the examination of the cerebrospinal fluid (CSF) after lumbar puncture for the presence of white blood cells (>5 cells/mL threshold), trypanosomes, or increased protein content (>370 mg/L) (1).

For the early-stage disease caused by *T b gambiense*, pentamidine is the drug of choice. Evidence for resistance of *T. gambiense* to pentamidine from the field is, at best, anecdotal. Treatment failures with pentamidine are rare and believed to usually constitute misdiagnosed late-stage disease. The lack of resistance is remarkable, as the drug has been used since 1940 and has been the first-line treatment for *T b gambiense* sleeping sickness for more than 60 years. Suramin is an alternative therapy in this setting, and it is also the standard treatment for early-stage *T b rhodesiense* disease. Currently, the first-line treatment recommended for the late, meningoencephalitic stage of *gambiense* HAT is the combination of nifurtimox and

eflornithine (NECT). Second choice is eflornitine IV or melarsoprol IV and prednisolone per os in the event of relapse after NECT or eflornitine.

Early stage *gambiense* disease is treated with intramuscular pentamidine given as daily injections over 7 to 10 days.

Pentamidine is the drug of choice for treatment of first stage disease caused by *T b gambiense*. It is given intramuscularly for a week, unless it can be given as an intravenous infusion in saline over 2 h. There is pharmacokinetic evidence that three injections might be equally effective. By contrast, the use of pentamidine in intermediate-stage disease (ie, up to ten or 20 white blood cells per µL in CSF) has produced equivocal outcomes and should not be generally recommended. In a recent MSF study from the Republic of Congo, the risk of treatment failure in patients with a CSF white cell count of 6–10 cells/mm³ was three times higher than in those with a count of 0–5 cells/mm³.

Treatment of Human African Trypanosomiasis due to T B gambiense
Search for studies in the literature using PubMed and Embase identified three recent studies on pentamidine in the treatment of HAT including two studies with paediatric populations, the third one providing no information on age. In all three studies pentamidine was administered a dose of 4 mg/kg IM injection once daily, and for 7-10 days.

Balasegaram M, et al. 2006 [15]
In 2002-03, the Republic of the Congo increased the threshold separating stage 1 and 2 cases of HAT from a cerebrospinal fluid (CSF) white cell count of 5 cells/mm3 to 10 cells/mm3. This retrospective study was aimed to assess whether the increased threshold of 10 cells/mm3 is a safe indicator of stage 2 disease. Patients of the study were treated for stage 1 HAT caused by T b gambiense in the Republic of the Congo between April 2001 and April 2005. Those with 0-10 cells/mm3 in CSF were classed as stage 1 and treated with pentamidine at a dose of 4 mg/kg IM injection once daily for 7 days; those with CSF of more than 10 cells/mm3 were classed as stage 2 and treated with either melarsoprol or eflornithine. The retrospective analysis involved all patients treated after the September 2002 increase in threshold for classification of HAT disease stage 2, and who were eligible for at least 1 year of follow-up. Primary outcome was survival without death or relapse within 1 year of discharge. Risk factors for treatment failure, in particular CSF white cell count on diagnosis, were assessed.
Between September 2002 to April 2004, 692 patients eligible for analysis were treated with pentamidine, including 148 patients (23%) aged less than 15 years. All were discharged alive after treatment with pentamidine, including 454 patients (66%) after 6 (±2) months of follow-up, and 371 patients (54%) after one year (±2 months) of follow-up. Relapse rate was 5% (n = 33). The only identified risk factor for relapse was a CSF white cell count of 6-10 cells/mm3 rather than 0-5 cells/mm3 (adjusted hazard ratio 3.27 (95% CI, 1.52-7.01); p = 0.002).

The authors concluded that overall, pentamidine was safe and well tolerated. However, a CSF white cell count of 10 cells/mm3 as the threshold between stage 1 and 2 seems to be associated with a higher risk of relapse. Thus a threshold of 5 white cells/mm3 in CSF is safer than 10 cells/mm3 to determine stage 2 HAT and reduce risk of relapse.

• **Simarro PP, et al. 2006 [16]**
After the resurgence of sleeping sickness in Luba, Equatorial Guinea, a major campaign to control the disease was established in 1985. The campaign comprised no vector control, but intensive active and passive surveillance using serology for screening (indirect immunofluorescent test, then CATT in 2000). Total prevalence was used to classify villages as endemic, at risk, anecdotal and non-endemic which also allowed defining the geographic extent

of the focus. Active case finding was implemented from 1985 to 2004. All cases underwent lumbar puncture to determine the stage of the disease. All parasitological and suspected serological cases were treated, first stage cases with pentamidine 4 mg/kg by IM injection once daily for 10 days, and second-stage cases with melarsoprol. A few relapses and very advanced cases were treated with eflornithine.
Regarding treatment, 615 cases were treated, including 582 new cases and 33 relapses. Data regarding age groups were not available. Of the 582 new cases, 267 were new first stage cases treated with pentamidine. In this group the relapse rate observed was 1.5%; all were retreated with melarsoprol. No fatalities were observed. A total of 341 cases were treated with melarsoprol, 311 were new second stage cases, and 13 were relapses (7 melarsoprol relapses, 4 pentamidine relapses, and 2 eflornitine relapses). The death rate because of sleeping sickness was 1.9%. The last case was identified and treated in 1995.
The authors concluded that control efforts focused on human reservoir by systematic and periodic case-finding surveys, with appropriate screening methodology, good coverage and the treatment of all detected cases, can rapidly reduce prevalence and transmission of the disease.

• **Eperon G, et al. 2007 [17]**
The aim of this retrospective study was to describe the demographic, clinical, diagnostic, treatment and outcome characteristics of HAT in pre-school children from Kajo-Keji County, South Sudan in comparison with older patients, from June 2000 to December 2002.
Of 1958 HAT patients, 119 (6.1%) were pre-school children (< 6 years) including 56 (47%) in first-stage illness and 63 (53%) in second-stage. The proportion of children in second-stage HAT was significantly higher in very young children (< 2 years). Walking and speech disturbances were more frequent in second-stage HAT but other neurological symptoms and signs were not associated with disease stage. Treatment outcome and adverse events were assessed in 54 preschool and 766 older patients with first-stage HAT treated with pentamidine isetionate 4 mg/kg daily for 7 days. Pentamidine treatment for first-stage illness was very safe and effective among pre-school children with no death or severe adverse events reported. In contrast, 4.9% of preschool children in second-stage illness died during melarsoprol treatment and 46% had one or more severe adverse event(s). Macular rash, jaundice and skin necrosis on injection site were significantly more frequent in this age group ($p < 0.05$). Melarsoprol-induced encephalopatic syndrome was less frequent but more severe than in older age groups.
In authors' opinion, the clinical features of *T. b. gambiense* HAT among pre-school children are insufficiently stage-specific. Therefore, laboratory-based staging is mandatory to prevent unnecessary harm to HAT patients caused by the high toxicity of melarsoprol.

Assessor's comments

Overall the reported studies fully supports the continued efficacy and safety of pentamidine for the treatment of first stage *T. b. gambiense* HAT in children. Based on the study by Balasegaram et al, it is essential to restrict pentamidine treatment to stage I patients, by excluding patients with a CSF count of > 5 cells. In contrast to PCP, in which AE associated with intravenous pentamidine are more frequently reported, the short term use of i.m. pentamidine in the treatment of leishmanappears to be generally better tolerated. However it is likely that the ascertainment of side effects in the African studies were less detailed compared to studies on PCP reported from industrialized countries. When given by intramuscular injection, site pain and transient swelling, abdominal pain and gastrointestinal problems, and hypoglycaemia (5–40%) are the most frequently reported pentamidine associated adverse events. Other important adverse drug reactions such as leucopenia, thrombocytopenia, hyperkalaemia, and QT-prolongation, which are seen in treatment of PCP were rarely reported, probably because of the scarcity of adequate methods for patient monitoring.

Safety

Pentamidine treatment is associated with several side effects. In fact, the incidence of severe adverse effects—diabetes mellitus, severe hypoglycaemia, hypotension,fever, myocarditis and renal toxicity may limit its use.

In contrast, inhalation of pentamidine is overall well tolerated, but can provoke bronchoconstriction and has been associated with pancreatitis and development of pneumothorax.

Pentamidine is usually administered intramuscularly for therapy of sleeping sickness. The drug is irritant to tissues and pronounced local pain is common with transient swelling or sterile abscesses.

Important adverse effects of pentamidine include hypoglycemia, hyperglycemia, and hypotension. Hypotension can be prevented by slow infusion of pentamidine. Cases of diabetes have been reported, particularly in patients receiving a cumulative of dose of greater than 2.0 g.

Gastrointestinal side-effects are common and include nausea, vomiting, sensation of bitter taste. Inhalation of pentamidine is associated with oral paresthesia.

Pentamidine may cause QT-prolongation, and torsades de pointes and cardiac arrest have been reported, also in children, and monitoring of QT is mandatory during iv treatment of PCP.

Haematological toxicity include bone marrow suppression e.g, leucopenia and thrombocytopenia.

Submitted pharmacovigilance data

On 12 October 2011, a cumulative search was performed in AWARE ™ using the MedDRA Version 14.0 to detect all adverse events occurring with pentamidine in the pediatric population defined as age of 17 years or less (including age categories of newborn, infant, child, and adolescent), reported prior to and including 11 October 2011. The search included all reporting sources that were received since first marketing of pentamidine (15 June 1988). A total of 32 pediatric cases were identified involving a total of 78 adverse events. Of the 32 cases, all were spontaneous reports. Of these 32 cases, most of the reports were serious (27 cases involving 72 events). Most of the reported cases (6) involved the SOC Renal and urinary disorders, and the SOC Respiratory, thoracic and mediastinal disorders (6 cases).
The most commonly reported events were: renal failure (4), and renal impairment (4). The ten most frequently reported adverse events during this reference period are tabulated below. This table includes adverse events from medically confirmed and medically unconfirmed case reports.

Table 1 - Summary table of the 10 most frequently reported adverse reactions (Period: 15 June 1988 to 11 October 2011)

MedDRA Preferred term	No of serious adverse reactions	No of non-serious reactions	Total
Renal failure acute	4	0	4
Renal impairment	4	0	4
Pancytopenia	3	0	3
Disseminated intravascular coagulation	2	0	2
Thrombocytopenia	2	0	2
Anaphylactic shock	2	0	2
Pathogen resistance	2	0	2
Overdose	2	0	2
Blood alkaline phosphatase increased	2	0	2
Diabetes mellitus	2	0	2

Table 2 - Summary of Cumulative Cases of Pediatric Cases with Pentamidine

Case Number Country Age/ Gender/ Source of Reporting	Indication for Pentamidine	(MedDRA PT term/s)	Reaction to Onset/ Duration of Treatment	Potential Confounding Factors or Concomitant Medications Medical History	sanofi-aventis Comment
200411669JP (Japan) 6 month/Male Health Care Professional (Serious)	Pneumocystis Carinii pneumonia	Pancytopenia, Renal impairment	Unknown Unknown	Sulfamethoxazole trimethoprim Not reported	The physician assessed neither pancytopenia nor renal impairment was related pentamidine.
200411810FR (France) 10 Year/Female Health Care Professional (Non-serious)	Prevention of Pneumocystis carinii	Photopsia	Unknown 1 day	Not reported Leukemia	After first dose of pentamidine aerosol this child experienced visual flash for about 30 minutes. No further information provided.
200712733JP (Japan) 12 Month/Male Health Care Professional (Serious)	Pneumocystis Carinii pneumonia	Pancreatitis acute	14 days 12 days	Acyclovir, prednisolone, methylprednisolone, panipenem, betamipron, midazolam, dexamethasone and sulfamethoxazole/trimethoprim Interstitial pneumonia, childhood dermatomyositis and continuous hemodiafiltration	This child received pentamidine and experienced increased pancrease enzyme. Surgery for ileal perforation was performed. Pancreas enzyme decreased with discontinuation of milk feeding. Concomitant medications provide an alternative explanation for the report event, since pancreatitis had occurred prior to pentamidine administration.
200510310EU (Ireland) 12 Month/Female Health Authority (Serious)	Hypogammaglobulinemia	Injection site phlebitis	1 day 1 day	Immunoglobulins	On the same day, the child received a pentamidine infusion she experienced a local phlebitis (site unspecified)
FR02-11708 (France) 9 Year/Male Health Authority (Serious)	Ill defined disorder (NOS)	Mucosal inflammation	15 days Unknown	Prednisolone, vincristine, calcium folinate, methotrexate and mercaptopurine Acute lymphoid leukemia, congenital anomaly of spine (NOS), infection during perinatal period and insufficient physiological development.	This child with ALL received pentamidine inhalation, 2 weeks later he experienced mucosal inflammation and skin irritation of buttocks. Underlying medical and concomitant therapies (chemotherapy agents) provide an

Case Number Country Age/ Gender/ Source of Reporting	Indication for Pentamidine	(MedDRA PT term/s)	Reaction to Onset/ Duration of Treatment	Potential Confounding Factors or Concomitant Medications Medical History	sanofi-aventis Comment
					alternative explanation for the mucosal inflammation.
200713334JP (Japan) 5 Month/Male Health care Professional (Serious)	Unknown	Acute hepatic failure	Unknown Unknown	Not reported Not reported	This infant who received pentamidine injection 4 mg/day (indication unspecified) and experienced fatal acute hepatic failure. The physician assessed the event was due to other drugs (unspecified), not pentamidine. No further information was available
200812750DE (Germany) 12 Year/Male Health care Professional (Serious)	Pneumocystis Carinii pneumonia	Chronic hepatic failure, Hepatotoxicity, Hepatic ischaemia, Cholestasis	5 days 5 days	Sulfamethoxazole-trimethoprim, meronem, fluconazole, cholesterol and triglyceride reducers (unspecified) Renal transplantation and chronic rejection reaction, vesicoureteral reflux, urosepsis, fistula, hemodialysis, nephrectomy, increased intraocular pressure, hypertensive crisis, anemia, metabolic acidosis, hyperuricemia, osteopenia, gastroenteritis, peribronchitis, transient psychosis, peripheral neuropathy, hypocalcaemia, cachexia.	This child with significant medical history received multiple medications including pentamidine and sulfamethoxazole + trimethoprime, then experienced an acute hepatic reaction leading to chronic liver failure. Concomitant medications provide an alternative explanation to the reported event.
DE01-00327 (Germany) 5 Month/Female Health care Professional (Serious)	Prophylactic treatment	Anaphylactic shock	1 day 1 day	Cefotaxime, miconazaole, antilymphocyte, immunoglobulin (horse), 3 weeks prior to this event the infant had a anaphylactic reaction while receiving sulfamethoxazole+trimethoprime AIDS	Following a pentamidine infusion the infant experienced, cardiac arrest, severe bronchial obstruction and urticaria. Treatment included O2, adrenaline infusion and prednisolone. No further information was provided.
200920749GDDC (Colombia)	Visceral leishmaniasis	Pathogen resistance, Drug	Unknown	Meglumine antimonite	Patient 1 of 2. The child had recurring

Case Number Country Age/ Gender/ Source of Reporting	Indication for Pentamidine	(MedDRA PT term/s)	Reaction to Onset/ Duration of Treatment	Potential Confounding Factors or Concomitant Medications Medical History	sanofi-aventis Comment
12 Month/Female Literature (Serious)		ineffective	21 days	Not reported	episodes of high intermittent fever, chills, sweating, generalized mucocutaneous pallor, adynamia, hyporexia, and progressive abdominal distention. The reported events of pathogen resistance and drug ineffective are difficult to assess. The therapy was recommended by experts so the resistance cannot be attributed to a resistant strain that survived a low initial dose. The mechanisms that precluded a good clinical response in this patient are unclear, because she did not manifest any of the clinical conditions that could normally result in relative resistance. Such as immunodeficiency, severe malnutrition or severe infection.
200920763GDDC (Colombia) 36 Month/Male Literature (Serious)	Visceral leishmaniasis	Pathogen resistance, Drug ineffective	Unknown 20 days	Meglumine antimonite Not reported	Patient 2 of 2. This child had recurring intermittent fever, paleness, adynamia, chills, anorexia, weight loss, increased abdominal perimeter, cough, rhinorrhea and tachypnea. The bone marrow aspirate was positive for Leishmania. Treatment was changed to pentamidine 18 days. Five months later he returned in poor condition. Marrow

Case Number Country Age/ Gender/ Source of Reporting	Indication for Pentamidine	(MedDRA PT term/s)	Reaction to Onset/ Duration of Treatment	Potential Confounding Factors or Concomitant Medications Medical History	sanofi-aventis Comment
					aspirate was repeated and was positive again. The mechanisms that precluded a good clinical response in this patient are unclear, because he did not manifest any of the clinical conditions that could normally result in relative resistance. Such as immunodeficiency, severe malnutrition or severe infection.
FR01-00004 (France) 6 Year/Male Health care Professional (Serious)	Leishmaniasis	Overdose, Hepatic failure, Renal failure,	27 days 13 days	Antimony meglumine Not reported	This child received pentamidine and experienced an overdose, hepatic and renal failure. No additional information was provided. Insufficient information to allow a complete assessment.
200911149JP (Japan) 8 Year/Male Health care Professional (Serious)	Pneumonia	Electrocardiogram QT prolonged	Unknown Unknown	Not reported Leukemia	This child received pentamidine for pneumonia and experienced QT prolonged. No additional information was provided. Insufficient information to allow a complete assessment.
JP01-00804 (Japan) 8 Year/Male Health care Professional (Serious)	Pneumocystis Carinii pneumonia	Blood alkaline phosphatase increased, Haemoglobin decreased, Thrombocytopenia, Aspartate aminotransferase increased, Blood urea increased, Hyperglycaemia, Hypocalcaemia	8 days 14 days	Minocycline, ceftazidime, cefoperazone sodium sulbactam sodium, morphine, sulfamethoxazole+trimethoprime, itraconazole and prednisone Acute lymphoblastic leukemia (ALL), bone marrow transplant	This child was started on pentamidine even though radiology did not reveal Pneumocystis Carinii pneumonia. Laboratory data revealed abnormalities associated with aggravation of ALL (terminal phase). Eight days after starting pentamidine

Case Number Country Age/ Gender/ Source of Reporting	Indication for Pentamidine	(MedDRA PT term/s)	Reaction to Onset/ Duration of Treatment	Potential Confounding Factors or Concomitant Medications Medical History	sanofi-aventis Comment
					he experienced thrombocytopenia, moderate alkaline phosphatase increased and mild hemoglobin decrease. Within a few days he further experienced mild ASAT increase, mild BUN increase, moderate hyperglycemia, moderate hypocalcemia and mild hychloremia. Over the next 4 days the patient's condition deteriorated and he died due to worsening of pneumonia. Underlying disease progression provides an alternative explanation for the fatality.
200411317JP (Japan) 17 Year/Female Health care Professional (Non-serious)	Prophylactic treatment	Blood lactate dehydrogenase increased, Cytomegalovirus infection	7.9 weeks Unknown	Methylprednisolone, mycophenolate mofetil, tacrolimus, lansoprazole, aluminium hydroxide gel/magnesium hydroxide, candesartan cilexetil, bufferin, miconazole nitrate, mosapride citrate, magnesium oxide, and adenosine Hemithyroidectomy, hypertension, chronic renal failure, gastritis, constipation, oral fungal infection, IGA nephropathy, renal transplant, hypertension and chronic renal failure.	This adolescent with significant medical history and multiple concomitant medications received pentamidine inhalation prophylactically then experienced blood lactate dehydrogenase increase and cytomegalovirus infection. No additional information was provided. Underlying medical and multiple concomitant medications provide an alternative explanation for the reported events.
200410156JP (Japan) 24 Month/Female Health care Professional	Interstitial pneumonia	Hypoglycaemia	14 days 11 days	Lenograstim, methylprednisolone, cefmetazole, ceftazidime amikacin, polyethylene glycol treated human	This child with significant medical history and concomitant therapies received

Case Number Country Age/ Gender/ Source of Reporting	Indication for Pentamidine	(MedDRA PT term/s)	Reaction to Onset/ Duration of Treatment	Potential Confounding Factors or Concomitant Medications Medical History	sanofi-aventis Comment
(Serious)				normal immunoglobulin, ulinastatin, granisetron hydrochloride, azasetron ramosetron and aminophylline Wilms tumor removal, bone marrow depression, blood transfusion	pentamidine for suspected carinii pneumonia and experienced hypoglycemia. Due to queasy and vomiting caused by radiotherapy for underlying disease and drug therapy, the patient's food intake amount was not enough, and this could have been one of the causes of the event.
200711857FR (France) 16 Year/Female Health Authority (Serious)	Bone marrow transplant	Hyperglycaemia, Proteinuria	5 days Unknown	Methylprednisolone, and cyclosporine Aplastic marrow, bone marrow transplant	This adolescent with medullar aplasia treated by bone marrow graft received pentamidine inhalation and experienced hyperglycemia. Co-suspect treatment with methylprednisolone provides an alternative explanation for the reported event.
GB01-04893 (United Kingdom) 10 Month/Male Health Authority (Serious)	Pneumocystis Carinii pneumonia	Hyponatraemia, Renal tubular disorder, Metabolic acidosis, Syncope	2 days 5 days	Sulfamethoxazole+trimethoprime, tazobactam, itraconazole, immunoglobulin human normal, vancomycin, methylprednisolone, meropenem, nystatin, ciprofloxacin, ganciclovir, amphotericin B, paracetamol and atovaquone Severe sex linked combined immunodeficiency with absence of T cells	Two days after this infant received pentamidine he experienced acute renal tubulopathy, hyponatremia, metabolic acidosis and collapse. Two days later pentamidine was discontinued. Acute renal tubulopathy, metabolic acidosis and collapse are labeled in for pentamidine. However, hyponatraemia is unlabeled.
2011SA043773 (France) 16 Year/Female	Unknown	Cerebral venous thrombosis, Convulsion,	2 days Unknown	Chlormadinone acetate, asparaginase, valacivclovir and	This adolescent received 7 injections of asparaginase

Case Number Country Age/ Gender/ Source of Reporting	Indication for Pentamidine	(MedDRA PT term/s)	Reaction to Onset/ Duration of Treatment	Potential Confounding Factors or Concomitant Medications Medical History	sanofi-aventis Comment
Health Authority (Serious)		Hemiparesis		fibrinogen Lymphoblastic leukemia (NOS)	which induced a coagulation disorder. She received one injection of factor I (fibrinogen) and one injection of antithrombin III. Pentamidine and valacivclovir were started. Two days later she experienced generalized convulsive with ocular revulsion. Treatment included clonazepam with improvement noted. However, she presented with left hemiparesia. Angio-MRI revealed a cerebral thrombophlebitis. Concomitant medications (i.e. asparaginase) provide a more likely explanation for the reported events.
2010SA015343 (Japan) 8 Year/Male Literature (Serious)	Interstitial pneumonia	Renal impairment, Pancreatitis	Unknown 5 days	Prednisolone, ciclosporin Nephrotic syndrome, minimal change disease, varicella, DIC and encephalitis	This child with steroid-resistant nephrotic syndrome complicated by pneumocystis pneumonia which required the introduction of peritoneal dialysis experienced aggravation of renal function and pancreatitis while receiving pentamidine. Underlying disease complicated by the pneumonia provides an alternative explanation for the reported event.
FR01-00003 (France) 30 Month/Male Health care Professional	Aplastic anaemia	Nephrotic syndrome, Diabetes mellitus,	12.6 weeks 11 Weeks	Antimony meglumine, Sodium stibogluconate Disease of blood and	This child received pentamidine and experienced nephritic syndrome, diabetes, and pancytopenia. No

Case Number Country Age/ Gender/ Source of Reporting	Indication for Pentamidine	(MedDRA PT term/s)	Reaction to Onset/ Duration of Treatment	Potential Confounding Factors or Concomitant Medications Medical History	sanofi-aventis Comment
(Serious)		Pancytopenia		blood forming organs unspecified	additional information was provided. Insufficient information to allow a complete assessment.
FR02-01316 (France) 24 Month/Male Health care Professional (Serious)	Pneumocystis Carinii pneumonia	Renal failure acute	13 days 14 days	Unknown Trisomy 21, leukemia	This child with trisomy 21 and cytomegalovirus infection received pentamidine for PCP. On day 13 of pentamidine therapy he experienced acute kidney failure with macroscopic hematuria which required peritoneal dialysis. Underlying Down's Syndrome with know medical issues could provide an alternative explanation for the reported event.
JP01-00011 (Japan) 5 Year/Female Health care Professional (Serious)	Ill defined disorder (NOS)	Renal impairment, Respiratory failure, Renal impairment,	4 days 10 days	Furosemide, minocycline, pancuronium, ketamine, dopamine, dobutamine, antilymphocyte immunoglobulin (horse)	This child received pentamidine and experienced renal impairment and respiratory failure. No additional information was provided. Insufficient information to allow a complete assessment.
JP01-00013 (Japan) 7 Year/Female Health care Professional (Serious)	Pneumocystis Carinii pneumonia	Renal failure acute, Disseminated intravascular coagulation,	Unknown 4 days	Unknown Acute lymphocytic leukemia	This child received pentamidine then experienced fatal renal failure and disseminated intravascular coagulation. No additional information was provided.
200020086JP (Japan) 16 Year/Male Literature (Serious)	Pneumocystis Carinii pneumonia	Obstructive airways disorder, Overdose	14 days 14 days	Bromhexine, blood Disseminated intravascular coagulation, renal failure, GI bleed,	This adolescent received an overdose of pentamidine (1800mg/day) via inhalation leading to aspiration and airway

Case Number Country Age/ Gender/ Source of Reporting	Indication for Pentamidine	(MedDRA PT term/s)	Reaction to Onset/ Duration of Treatment	Potential Confounding Factors or Concomitant Medications Medical History	sanofi-aventis Comment
				liver disorder, systemic lupus erythematosus	obstruction. Adherence of the pentamidine inside the endotracheal tube and a significant overdose, contributed to the plug formation, along with thick secretions and sputum from the underlying infection.
200211279JP (Japan) 11 Year/Female Health care Professional (Serious)	Pneumocystis Carinii pneumonia	Cough, Oropharyngeal pain, Dysphonia	7 days 8 days	Orciprenaline sulfate, bromhexine, sulfamethoxazole+trimethoprime Not reported	This child received orciprenaline sulfate, bromhexine prior to pentamidine, then experienced severe cough, moderate pain pharynx and moderate hoarseness. The reported events were improved with throat lozenge therapy. Concomitant medications provide an alternative explanation to the reported event.
200622269GDDC Switzerland 12 Year/ Female Literature (Serious)	Unknown	Pulmonary embolism	Unknown Unknown	Immunosuppressive agents, corticosteroids, plasmapheresis Multiple sclerosis, obesity, subclavian catheterization	This child with significant medical history received pentamidine inhalation and immediately experienced sudden palpitation, dyspnea and speech difficulty without pruritus, tongue swelling or skin rash. She was treated with alteplase for a blocked subclavian dialysis catheter. In view of the rapid onset of her illness and the presence of a partially working dialysis catheter, pulmonary embolus (PE) was strongly suspected. D-dimers (ELISA) were elevated. Heparin was started and

Case Number Country Age/ Gender/ Source of Reporting	Indication for Pentamidine	(MedDRA PT term/s)	Reaction to Onset/ Duration of Treatment	Potential Confounding Factors or Concomitant Medications Medical History	sanofi-aventis Comment
					switched to warfarin after 6 days. Underlying multiple sclerosis (sedentary), steroids, and partially working dialysis catheter predisposing this patient to a hypercoagulable state and thus leading to a PE.
200811265JP (Japan) 14 Year/Male Health care Professional (Non-serious)	Pneumocystis Carinii pneumonia	Respiratory disorder	21 days 15 days	Not reported Not reported	This adolescent experienced respiratory rate decreased after receiving pentamidine inhalation for PCP. No additional information was provided. Insufficient information to allow a complete assessment.
2010SA012478 (Japan) 12 Year/Male Health care Professional (Non-serious)	Unknown	Respiratory tract irritation	Unknown Unknown	Not reported Not reported	This child experienced a strange sensation in his airway after receiving pentamidine (inhalation). No additional information was provided. Insufficient information to allow a complete assessment.
GB01-01041 (United Kingdom) 9 Year/Female Health care Professional (Non-serious)	Pneumocystis Carinii pneumonia	Dyspnoea	Unknown Unknown	Piperacillin sodium/tazobactam sodium, gentamicin, clarithromycin, clotrimazole, ranitidine, lactulose, folic acid, amikacin, acyclovir, spironolactone, amphotericin Not reported	This child experienced two moderate episodes of shortness of breath after receiving pentamidine IV. The non serious event resolved with nebulizer salbutamol. No additional information was provided.
200511884FR (France) 13 Year/Male Health Authority (Serious)	Prophylactic treatment	Rash	5 weeks Unknown	Ritonavir, nevirapine, tenofovir disoproxil fumarate, telzir,	This adolescent on multiple anti viral medications experienced a rash while receiving

Case Number Country Age/ Gender/ Source of Reporting	Indication for Pentamidine	(MedDRA PT term/s)	Reaction to Onset/ Duration of Treatment	Potential Confounding Factors or Concomitant Medications Medical History	sanofi-aventis Comment
				Mother was seropositive for HIV during pregnancy and not treated. Rash bullous, and HIV infection.	pentamidine (inhalation). All medications were continued. Concomitant medications and the underlying disease provide a more likely explanation for the event. Eruption is listed for pentamidine inhalation route.
DE01-00333 Germany 24 Month/Female Health care Professional (Serious)	Pneumocystis Carinii pneumonia	Angioedema	Unknown Unknown	Not reported AIDS, allergy to cotrimoxazol	This child experienced severe Quinke edema 15 minutes after injection of pentamidine. No additional information was provided. Insufficient information to allow a complete assessment.
200813119FR (France) 17 Year/Female Health Authority (Serious)	Unknown	Infarction	Unknown Unknown	Omeprazole, valaciclovir, clarithromycin, immunoglobulin, tacrolimus, sirolimus, mycophenolate, bisoprolol fumarate, ursodeoxycholic acid, spironolactone, betamethasone sodium, furosemide T-lymphoblastic lymphoma leukemia, acute graft versus host disease	This adolescent received pentamidine (indication unspecified) and experienced fatal infarction. Underlying acute T-lymphoblastic leukaemia complicated by chronic graft versus host disease, and several other drugs, may provide alternative explanations

MAH conclusion: Based on the information available, the adverse drug reactions reported were either listed for pentamidine treatment, confounded by risk factors or caused by other known underlying diseases, or provided insufficient information for medical assessment. There are no new safety concerns identified regarding the use of pentamidine in children at present.

Assessor's comments

The MAH conclusion is supported. The reported AE/SAE's show a range of the commonly known adverse effects associated with pentamidine treatment, which is usually used in patients with severe comorbidity and immunosuppression. The reported cases of QT-prolongation and the severity of AE highlight the possible severe toxicity of pentamidine.

Three issues have been identified:

1. The MAH has omitted mention of a recently reported side effect associated with pentamidine use in children. Brown and co-authors recently reported 4 cases of pentamidine associated parasthesias in pediatric patients and 1 case in a young adult [18] . In this report, all 5 patients received i.v. pentamidine (4 mg/kg) over 1 hour. The patients experienced a range of symptoms, including facial numbness, perioral numbness, and extremity parasthesias. The symptoms occurred at the end of the infusion or immediately post infusion in 4 of the cases. One patient developed perioral numbness and parasthesias in his left hand 15 minutes into the infusion. All episodes resolved within 30 minutes of completion or interruption of the infusion. Each patient was able to complete the infusion.

The MAH is requested to provide other information regarding pentamidine associated parasthesias and should update the SPC with information regarding this side effect.

2. The pathogenic basis for the quite variable incidence of pentamidine associated toxicity is unknown. In a recent study by Afrin et al, the authors suggest that genetic polymorphism in CYP2C19 affecting the human metabolism of pentamidine may play an important role if impaired pentamidine clearance caused by differences in this gene could result in toxicity ordinarily expected only with high dose pentamidine [19]. The authors speculate that genotyping before prophylaxis or treatment in theory could prevent major toxicity of pentamidine if patients with decreased clearance could be identified for alternative treatments.

The MAH is requested to discuss this paper and the possible clinical value of CYP2C19 genotyping for the management of pentamidine associated toxicity

3. Intramuscular administration of pentamidine is associated with pain and sterile abscesses. While intramuscular treatment is acceptable for the treatment of leishmania and trypanosomiasis, intramuscular treatment with pentamidine cannot be recommended for PCP. Some of the current EU SPCs are unclear regarding the recommendation of im or iv administration for PCP (e.g Spain). It is proposed to harmonize the current SPC on this matter.

IV.2 RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION IN PRELIMINARY PAEDIATRIC AR

➢ Overall conclusion

Pentamidine is infrequently used and there is overall quite limited data on the paediatric use. This updated review provides very few new data. Although pentamidine is associated with significant side effects, this agent remains a valuable treatment option in children for second or third line treatment of PCP, prophylaxis of PCP in patients intolerant of TMP-SMX and has a restricted but important role for the treatment of HAT and certain forms of leishmaniasis.

In conclusion, the overall benefit/risk ratio for pentamidine solution for injection and nebuliser for the treatment and prophtlaxis of PCP, HAT stage I and certain forms of leishmaniasis remains favourable.

➢ Recommendation

1. The Rapporteur recommends that the EU SPCs are harmonised with regards to:
   - The MAH propose to harmonize the SPCs in regard to the dosing interval for the trypanosomiasis indication, to include in all SPCs the option of once daily dosing. The wording in the dosage section would then read "4 mg/kg body weight once daily or every other day up to a total number of 7-10 doses". This proposal is supported.
   - Intramuscular treatment of PCP is not acceptable, the SPCs should clearly indicate that only iv treatment is recommended for PCP
   - Pentamidine associated parasthesias have been recently described among pediatric patients receiving intravenous pentamidine. The MAH should discuss this side-effect and update 4.8 with this information.

2. The possibility that genetic polymorphism in CYP2C19 may contribute to pentamidine associated toxicity has recently been suggested. The MAH is requested to discuss this finding

3. The current SPCs from Germany, UK and Ireland still contains the long obsolete indication that inhalation of pentamidine can be used for the *treatment* in mild cases of PCP. Inhaled pentamidine was clearly proven inferior to the standard treatment of PCP by TMP/SMX (oral or iv) or intravenous pentamidine in the early eighties and cannot in this assessors opinion be recommended for the treatment of PCP. The Rapporteur recommends that this indication is deleted for both children and adults. Deletion of the indication is however not considered within the scope of this paediatric worksharing procedure.

IV.3 REQUEST FOR SUPPLEMENTARY INFORMATION IN PRELIMINARY PAEDIATRIC AR

List of questions:

1. The MAH has omitted mention of a recently reported side effect associated with pentamidine use in children. Brown and co-authors recently reported 4 cases of pentamidine associated parasthesias in pediatric patients and 1 case in a young adult. In this report, all 5 patients received i.v. pentamidine (4 mg/kg) over 1 hour. The patients experienced a range of symptoms,

including facial numbness, perioral numbness, and extremity parasthesias. The symptoms occurred at the end of the infusion or immediately post infusion in 4 of the cases. One patient developed perioral numbness and parasthesias in his left hand 15 minutes into the infusion. All episodes resolved within 30 minutes of completion or interruption of the infusion. Each patient was able to complete the infusion.
The MAH is requested to provide other information regarding pentamidine associated parasthesias and should update the SPC with information regarding this side effect.

2. The pathogenic basis for the quite variable incidence of pentamidine associated toxicity is unknown. In a recent study by Afrin et al, the authors suggest that genetic polymorphism in CYP2C19 affecting the human metabolism of pentamidine may play an important role if impaired pentamidine clearance caused by differences in this gene could result in toxicity ordinarily expected only with high dose pentamidine. The authors speculate that genotyping before prophylaxis or treatment in theory could prevent major toxicity of pentamidine if patients with decreased clearance could be identified for alternative treatments.
The MAH is requested to discuss this paper and the possible clinical value of CYP2C19 genotyping for the management of pentamidine associated toxicity

3. The MAH is requested to provide a proposal for PL text corresponding to the proposed harmonized SPC wordings.

IV.4 RAPPORTEUR'S SSESSMENT OF MAH RESPONSE TO QUESTIONS IN THE PRELIMINARY PAEDIATRIC AR / MS COMMENTS DAY 85

Following the Danish Pediatric work sharing Preliminary Assessment Report on Pentamidine, a reply to the issues raised have been received from the MAH, Sanofi as well as comments from the MS, Netherlands (NL) and Sweden (SE).

The MAH is requested to provide a proposal for PL text corresponding to the proposed harmonized SPC wordings.

The currently approved EU SPCs have several differences with regards to indications – it is proposed to harmonize the SPCs with regards to:

Indication for use in PCP.

The current SPCs from Germany, UK and Ireland still contains the long obsolete indication that inhalation of pentamidine can be used for the treatment in mild cases of PCP. Inhaled pentamidine was clearly proven inferior to the standard treatment of PCP by TMP/SMX (oral or iv) or intravenous pentamidine in the early eighties and cannot in this assessors opinion be recommended for the treatment of PCP. It is suggested that this part of the indication is deleted for both children and adults.

Trypanosomiasis indication

The MAH propose to harmonize the SPCs in regard to the dosing interval for the trypanosomiasis indication, to include in all SPCs the option of once daily dosing. The wording in the dosage section would then read "4 mg/kg body weight once daily or every other day up to a total number of 7-10 doses". This proposal is supported.

Comments from Netherlands:

- *In the Netherlands, no paediatric posology has been approved. The MEB however remarks that the above mentioned recommendations should not be limited to use in children, as these recommendations also apply for adults. The MAH is recommended to submit a variation application for these SPC changes regarding use in adults also.*

- *Regarding paediatric posology, the MEB is of opinion that based on the available data no specific recommendations can be made on the correct posology in paediatric patients for both formulations. Treatment of pneumocystis pneumonia with intravenous Pentamidine has primarily been studied in adults and efficacy and safety data for pentamidine has to be extrapolated from adults. Similarly, inhalational Pentamidine has not been systematically evaluated in children in the adult dosage or any other dosage. Therefore, these extrapolations using the adult dosage, although they have been included in guidelines as second or third line options, cannot formally be supported.*

Any modification / harmonization of indications or their (paediatric) dose recommendations should be discussed in another setting which could also result in consensus on modification of the SPC.

Comments from Sweden:

SE agrees that intramuscular pentamidine treatment of PCP is not acceptable, but SE is also of the opinion that intravenous administration should be the preferred way of pentamidine treatment of trypanosomiasis and leishmaniasis within the EU, where patients can be closely monitored during drug therapy. The risks associated with i.v. pentamidine administration can thus be avoided as well as the adverse effects of pentamidine given intramuscularly.

Sanofi response:

SmPC update

As proposed already by the company and endorsed by the rapporteur, the SmPCs will be harmonized in regard to the dosing interval for the tryponosomiasis indication, to include in all SmPCs (where this is not yet included) the option of once daily dosing, which is the preferred regimen endorsed by the World Health Organization (WHO), Médecins Sans Frontières (MSF), and the Centers for Disease Control and Prevention (CDC).
The specific wording proposed to be added in all SmPCs would then read (new text underlined):
“4mg/kg body weight once daily or every other day up to a number of 7-10 doses”

Since the SmPCs in the individual European countries will be updated locally, no specific wording is proposed for further harmonization of labeling texts. However, the company agrees with the recommendations as outlined in the assessment report, and will issue a Global Labeling Update (GLU) to address the rapporteur’s recommendations in regard to the preferred route of administration for the treatment of PCP and to restrict the inhalation route to prophylaxis of PCP only.

As for the member comment from Sweden in regard to the recommendation to make the IV administration also the preferred route of administration for the indications trypanosomiasis and leishmaniasis, the company does not disagree with the assessment that the IV administration is the preferred route of administration in case adequate close monitoring is guaranteed. However, since the availability of close monitoring of patients is probably difficult to predict for all health care settings on a worldwide basis, and since the IM route is well established in many international countries, the company proposes not to change the current approved route of administration in local SmPCs. However, if a decision is made on local level to make a

recommendation as per the preferred route taking into account country specific considerations and guidelines, the MAH would not be opposed to such an approach.

As for the member state comment from the Netherlands, the MAH agrees that the above mentioned SPC updates apply to adults as well as children.

Regarding the pediatric posology, it is acknowledged that the pediatric dosage recommendations are extrapolated using adult dosage, and that data are limited in children, especially in regard to the inhalation route. It is also acknowledged that a modification/ harmonization of indications and pediatric dose recommendations are not in the scope of this Art 45 procedure and should be discussed in another setting.

Assessor's comments
Sanofi now accepts a harmonization in regard to the dosing interval for the trypanosomiasis indication by including in all SmPCs (where this is not yet included) the option of <u>once daily</u> dosing. This issue is therefore resolved.

The company agrees to issue a Global Labeling Update (GLU) in regard to the preferred route of administration for the treatment of PCP and to restrict the inhalation route to prophylaxis of PCP only. This is acceptable and the issue is resolved.

Regarding the issue of i.v vs. i.m. administration of pentamidine for trypanosomiasis and leishmaniasis raised by SE, the company proposes not to change the current approved route of administration in local SmPCs as the availability of close monitoring of patients is probably difficult to predict for all health care settings on a worldwide basis, and since the IM route is well established in many international countries. This seems overall acceptable.

<u>Question 1.</u>

The MAH has omitted mention of a recently reported side effect associated with pentamidine use in children. Brown and co-authors recently reported 4 cases of pentamidine associated parasthesias in pediatric patients and 1 case in a young adult.

In this report, all 5 patients received i.v. pentamidine (4 mg/kg) over 1 hour. The patients experienced a range of symptoms, including facial numbness, perioral numbness, and extremity parasthesias. The symptoms occurred at the end of the infusion or immediately post infusion in 4 of the cases. One patient developed perioral numbness and parasthesias in his left hand 15 minutes into the infusion. All episodes resolved within 30 minutes of completion or interruption of the infusion. Each patient was able to complete the infusion.

The MAH is requested to provide other information regarding pentamidine associated parasthesias and should update the SPC with information regarding this side effect.

<u>Sanofi response:</u>

In consideration of the recent concern regarding pentamidine associated paresthesias sanofi explored this side-effect, including a cumulative search for all cases in sanofi internal safety database. The search indentified 7 cases of paresthesia and 1 case of burning sensation; and 6 reports of hypoesthesia, which included the cases mentioned in Brown article(1). In addition, a cumulative search on global literature sources, and the relevant textbooks were also searched, which also found description of pentamidine associated paresthesia and hypoesthesia(2)(3)(4)(5).

Following analysis on the information available, it was concluded that there are sufficient evidences to support a causal relationship between pentamidine iv treatment and extremity paresthesia, and perioral and facial hypoesthesia in pediatric and adult patients.

Proposed SmPC update

The MAH agrees to update the local SmPCs to include labeling wording on paresthesia in section 4.8 (Undesirable effects section) of the Pentamidine SmPCs. A Global Labeling Update will be issued with the following wording, applicable to the IV administration only, to be included in all SmPCs:

"Extremity paresthesia as well as perioral and facial hypoesthesia have been reported with IV administration of pentamidine, both in children and adults. The cases occurred during or shortly after the IV infusion and resolved after completion or interruption of the infusion."

Assessor's comments
Issue resolved, the proposed update to the SmPC 4.8 is accepted.

Question 2

The pathogenic basis for the quite variable incidence of pentamidine associated toxicity is unknown. In a recent study by Afrin et al, the authors suggest that genetic polymorphism in CYP2C19 affecting the human metabolism of pentamidine may play an important role if impaired pentamidine clearance caused by differences in this gene could result in toxicity ordinarily expected only with high dose pentamidine. The authors speculate that genotyping before prophylaxis or treatment in theory could prevent major toxicity of pentamidine if patients with decreased clearance could be identified for alternative treatments.
The MAH is requested to discuss this paper and the possible clinical value of CYP2C19 genotyping for the management of pentamidine associated toxicity

Sanofi response:

The study by Afrin et al is a cost analysis, in which the authors reviewed the charts of 32 allogeneic stem cell transplant (alloSCT) patients receiving pentamidine. The study did not associate toxicity with pentamidine exposure or with CYP2C19 genotype. Genotyping was performed on only one patient. The study did not associate pentamidine exposure with CYP2C19 genotype nor did it reference studies associating pentamidine exposure with CYP2C19 genotype. This was neither a randomized controlled trial nor a cohort study.

Pentamidine Metabolism

The references used in Afrin et al do not support the statement "Humans depend almost exclusively upon cytochrome P450 2C19 (CYP2C19) to metabolize pentamidine" (6)(7). These references simply state that pentamidine is a substrate of CYP2C19, and reference *in vitro* studies in human liver microsomes to support this statement (8). There is no supportive evidence for the fraction metabolized by CYP2C19 or clinical evidence that CYP2C19 is primarily responsible for the metabolic hepatic clearance of pentamidine in humans. Several authors have implicated other CYP enzymes in the *in vitro* metabolism of pentamidine, including CYPs 1A1, 2A6, 2D6, 3A5 and 4A11 (8)(9)(10). No definitive human studies have identified

CYP2C19 as the predominant drug metabolizing enzyme responsible for pentamidine clearance or associated pentamidine exposure to CYP2C19 genotype.

It is our contention that Afrin et al does not support prospective CYP2C19 genotyping for the management of pentamidine associated toxicity.

This response was supported by literature searches performed in Medline, Embase, PubMed (1980 - present), The University of Washington Drug Interaction Data Base and Google Scholar. Keywords: pentamidine, metabolism, CYP2C19, pharmacokinetics, cytochrome P450, pharmacogenetics, pharmacogenomics

As a result, no SmPC changes are being proposed at this time.

Assessor's comments
The MAH response is accepted, based on the response the issue is resolved, no SmPC changes.

IV.5 RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION IN FINAL PAEDIATRIC AR

Overall conclusion
Based on this review, the issues on Pentamidine for pediatric use have been adequately resolved.

Recommendation
The recommendations as outlined in this assessment report are generally not considered within the scope of the article 45 paediatric worksharing procedure. The recommendations should not be limited to use in children, as these also apply for adults. The company has agreed to issue a Global Labeling Update (GLU) to address the recommendations, which is accepted by the Rapporteur.

Request for supplementary information
Not applicable

IV.6 ASSESSMENT OF RESPONSE TO QUESTIONS FROM FR DAY 115

Following the Danish Pediatric work sharing Final Assessment Report on Pentamidine comments were received from the MS, France (FR).

Comments from France:
We anticipate some difficulties in implementing the conclusion of the pdWS since this may will have impact on the dosing recommendation in adults while there is no clear message across EU SPC on the optimal mode of administration of pentamidine depending on the indication.

Before the finalisation process, the applicant should be asked to discuss the current state of the art in terms of mode of administration (IM or IV) depending on the indication.

Assessor's comments
We are of the opinion that such discussion is not within the scope of this paediatric worksharing procedure.
In the FPdAR it is stated that since the recommendations given are not limited to use in children, but also apply for adults, a type IB variation to implement the wording following paediatric worksharing procedure is not proposed. The applicant has agreed to issue a Global Labeling Update, which is accepted by the Rapporteur.

Sanofi response:
We confirm you that an update of labeling accross Europe will be done after finalisation of the Article 45 procedure (and PSUR worksharing procedure also on-going at the moment).

As stated in our response dossier, the company agrees with the recommendations as outlined in the assessment report in regard to the preferred route of administration for the treatment of PCP and to restrict the inhalation route to prophylaxis of PCP only.

The company intends to ask each European country to update their local labeling according to the following recommendations:
The local PIs should clearly indicate that IV treatment is the preferred route of administration for the treatment of PCP.
The inhalation route is not recommended for the treatment of mild PCP and should be removed from all PIs, where this recommendation is still included. The IV route is considered the preferred route of administration for the treatment of PCP. The inhalation route should be used for prophylaxis of PCP only

Assessor's comments
We agree with the proposed commitment. Moreover we would appreciate that the MAH would be requested to discuss in the next submitted labelling variation the current state of the art in terms of mode of administration (IM or IV) for the other authorised indications: trypanosomiasis and leishmaniasis.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

Overall conclusion
Based on this review, the issues on Pentamidine for pediatric use have been adequately resolved.

Recommendation
The recommendations as outlined in this assessment report are generally not considered within the scope of the article 45 paediatric worksharing procedure. The recommendations should not be limited to use in children, as these also apply for adults. The company has agreed to initiate variations to address the recommendations in order to achieve a harmonized position in EU.

The company intends to ask each European country to update their local labeling according to the following recommendations:
The local PIs should clearly indicate that IV treatment is the preferred route of administration for the treatment of PCP.
The inhalation route is not recommended for the treatment of mild PCP and should be removed from all PIs, where this recommendation is still included. The IV route is considered the preferred route of administration for the treatment of PCP. The inhalation route should be used for prophylaxis of PCP only.
This is accepted by the Rapporteur.

The company is also recommended to discuss in the next submitted labelling variation the current state of the art in terms of mode of administration (IM or IV) for the other authorised indications: trypanosomiasis and leishmaniasis.

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

Not applicable

VII. LIST OF MEDICINCAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

The list can be taken from the spreadsheet compiled from the EMA

MAH	MS	Name of the medicinal product	Strength	Pharmaceutical form
AVENTIS PHARMA DAGENHAM	ES	PENTACARINAT AEROSOL	300 mg	solution for injection
AVENTIS PHARMA DAGENHAM	ES	PENTACARINAT INYECTABLE	300 mg	powder for solution for injection
AVENTIS PHARMA SA NV	LU	PENTACARINAT 300	300 mg	powder for solution for injection
May & Baker Ltd	UK	PENTAMIDINE INJECTION 200MG	200 mg	powder for solution for injection
May & Baker Ltd	IT	PENTACARINAT	300 mg	powder for solution for injection and aerosol
SANOFI-AVENTIS BELGIUM	BE	PENTACARINAT 300	300 mg	powder for solution for injection
SANOFI-AVENTIS DEUTSCHLAND GMBH	DE	PENTACARINAT 200 MG	200 mg	powder for solution for injection

SANOFI-AVENTIS DEUTSCHLAND GMBH	DE	PENTACARINAT 300 MG	300 mg	powder for solution for injection
SANOFI-AVENTIS DENMARK A_S	DK	PENTACARINAT	200 mg	powder for solution for injection
SANOFI-AVENTIS DENMARK A_S	DK	PENTACARINAT	300 mg	powder for solution for injection
SANOFI-AVENTIS NETHERLANDS BV	NL	PENTACARINAT 300	300 mg	powder for solution for injection
Aventis Pharma Ltd	UK	PENTACARINAT 300 MG	300 mg	powder for solution for injection
Aventis Pharma Ltd	UK	PENTACARINAT READY-TO-USE SOLUTION 300MG	300 mg	solution for injection