HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

20 July 2011

METHYLTHIONINIUM CHLORIDE PROVEBLUE 5 mg/mL, solution for injection
Box containing 5 glass ampoules, CIP code: 580 083-4

Applicant: INRESA

methylthioninium chloride
ATC code: V03AB17 (antidote)

List I

Date of Marketing Authorisation (centralised procedure): 6 May 2011
Has had temporary authorisation for use (ATU) on a cohort basis since 22 November 2010.

Reason for request: Inclusion on the list of medicines approved for hospital use.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient:
Methylthioninium chloride

1.2. Background
The method for producing methylthioninium chloride or "methylene blue" uses a synthesis pathway that does not involve heavy metals.

1.3. Indication
"Acute symptomatic treatment of medicinal and chemical products- induced methaemoglobinaemia.
METHYLTHIONINIUM CHLORIDE PROVEBLUE is indicated in adults, children and adolescents (aged 0 to 17 years old)".

1.4. Dosage and method of administration
"METHYLTHIONINIUM CHLORIDE PROVEBLUE is for administration by a healthcare professional.

Dosage

Adults: The usual dose is 1 to 2 mg per kg body weight, i.e. 0.2-0.4 ml per kg body weight, given over a period of 5 minutes.
A repeat dose (1 to 2 mg/kg body weight, i.e. 0.2-0.4 ml/kg body weight) may be given one hour after the first dose in cases of persistent or recurrent symptoms or if methaemoglobin levels remain significantly higher than the normal clinical range.
Treatment does not usually exceed one day.
The maximum recommended cumulative dose for the course of treatment is 7 mg/kg and should not be exceeded, since METHYLTHIONINIUM CHLORIDE PROVEBLUE administered above the maximum dose may cause methaemoglobinaemia in susceptible patients.
In the case of aniline- or dapsone-induced methaemaglobinaemia, the maximum recommended cumulative dose for the course of treatment is 4 mg/kg.
The available data are too limited to support a continuous infusion dose recommendation

Special populations

Elderly No dose adjustment is necessary.

Renal impairment: METHYLTHIONINIUM CHLORIDE PROVEBLUE should be used with caution in patients with moderate to severe renal disease since there is limited data available and methylthioninium chloride is predominantly renally eliminated. Lower doses (<1 mg/kg) may be needed.

Hepatic impairment: There is no experience in patients with severe hepatic impairment.

Paediatric population:

Infants above 3 months, children and adolescents: Same dosage as for adults.
Infants 3 months old or younger and newborn infants: The recommended dose is 0.3-0.5 mg/kg body weight, i.e. 0.06 to 0.1 ml/kg body weight, given over a period of 5 minutes.
A repeat dose (0.3 to 0.5 mg/kg body weight, i.e. 0.06-0.1 ml/kg body weight) may be given one hour after the first dose in cases of persistent or recurrent of symptoms or if methaemoglobin levels remain significantly higher than the normal clinical range.
Treatment does not usually exceed one day.

Method of administration
Intravenous route.
METHYLTHIONINIUM CHLORIDE PROVEBLUE is hypotonic and may be diluted in 50 ml glucose to 50 mg/ml (5%) solution for injection to avoid local pain, in particular in paediatric population.
It must be injected very slowly over a period of 5 minutes.
It must not be administered by subcutaneous or intrathecal injection."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

V:	Various
V03:	All other therapeutic products
V03A:	All other therapeutic products
V03AB:	Antidotes
V03AB17:	Methylthioninium chloride

2.2. Medicines in the same therapeutic category

MARTINDALE methylene blue, which does not have Marketing Authorisation in France.

Ascorbic acid (vitamin C), n-acetylcysteine and tocopherol, which are also used in the management of methaemoglobinaemia but which do not have marketing authorisation for this indication.

2.3. Medicines with a similar therapeutic aim

Other therapeutic agents used in cases of poisoning:

- CYANOKIT 2.5 g, indicated for cyanide poisoning

Oxygen therapy and exchange transfusion are also used in the management of poisoning.

3. ANALYSIS OF AVAILABLE DATA

AGUETTANT methylene blue was marketed from January 1995. From March 2009, in order to alleviate the shortage of this product, arrangements were made to import MARTINDALE methylene blue in order to supply the French market until November 2010. On 17 November 2010, AFSSAPS received notification that AGUETTANT methylene blue would no longer be marketed, and temporary usage authorisation (ATU) on a cohort basis was granted to PROVEBLUE METHYLTHIONINIUM CHLORIDE on 22 November 2010.
PROVEBLUE METHYLTHIONINIUM CHLORIDE is intended to replace AGUETTANT methylene blue.

Evaluation of the efficacy and safety of methylthioninium chloride (methylene blue) was based on a literature review of 57 articles published between 1935 and 2010, containing data about the efficacy of methylene blue (methylthioninium chloride) in the management of poisoning involving chemical products and/or medicines, and an unpublished survey of poison centres.

Among these 57 publications, there were:

- three non-comparative clinical studies:
  These three open-label studies involving no comparator product evaluated the efficacy of methylthioninium chloride in a total of 39 children with methaemoglobinaemia caused by drugs (two studies) or chemical products (one study); two of these studies were retrospective (Bucharetchi 2000[1] and Sanchez-Echaniz 2001[2]) and the third was randomised (Prasad 2008[3]).
  The aim of the Sanchez-Echaniz study was to determine the clinical and epidemiological characteristics of seven children with beet-induced methaemoglobinaemia who were admitted urgently to a paediatric ward between 1993 and 1998; evaluation of the efficacy of methylene blue on methaemoglobin levels was not an objective of this study, and it therefore will not be described in detail in this opinion.

- 54 clinical cases (35 in adults and 19 in children), which will not be presented in this opinion (these are given in appendix 2, for information).

Finally, a survey of poison centres has also been submitted; this shows that methylene blue is the first-line treatment in the treatment of methaemoglobinaemia caused by medicines or chemical products (see appendix 1).

3.1. Efficacy

3.1.1. Bucaretchi 2000[1]

The objective of this retrospective open-label non-comparative study was to evaluate the efficacy of administration of activated charcoal in 17 children with methaemoglobinaemia > 20% caused by exposure to dapsone (an antibiotic). Fourteen of these children had a methaemoglobin level of > 30%.

1 Bucaretchi F et al. Acute dapsone exposure and methemoglobinemia in children: treatment with multiple doses of activated charcoal with or without the administration of methylene blue. Jornal de Pediatria 2000; 76: 290-4.
2 Sanchez-Echaniz J et al. Methemoglobinemia and consumption of vegetables in infants. Pediatrics 2001; 107: 1024-8.
3 Prasad R et al. Dapsone induced methemoglobinemia: intermittent vs continuous intravenous methylene blue therapy. Indian J Pediatr 2008; 75: 245-7.

Mean methaemoglobin level at the time of inclusion was 37.8%.

All the patients received several (3-16) doses of activated charcoal (median: 8 doses) and the 12/14 patients included who had methaemoglobin > 30% were also treated with methylene blue.

Primary efficacy endpoint: reduction in methaemoglobin levels.

Results:
After administration of several doses of activated charcoal, methaemoglobin fell to <15% in all patients treated; in the 12 patients whose treatment methylene blue was added, the fall was of the same order of magnitude and no statistically significant difference was observed between the "activated charcoal alone" and "activated charcoal + methylene blue" arms, p=0.49.

3.1.2. Prasad Study 2008[3]
The objective of this randomised study was to compare intermittent administration of methylene blue (2 mg/kg/dose every 6 hours) with continuous administration (2 mg/kg continuously) in terms of reduction in methaemoglobin levels in 11 children with methaemoglobinaemia caused by ingestion of dapsone.

A significantly greater reduction in methaemoglobin levels was observed for continuous treatment in comparison with intermittent treatment from 12 hours and up to 72 hours.

3.1.3. Survey of poison centres
The results of this survey, which are presented as an appendix to this opinion, show that methylene blue is the first-line treatment for methaemoglobinaemia caused by medicines or chemical products.

3.2. Adverse effects
According to the SPC, the most commonly observed adverse events are: nausea, abdominal and chest pain, headaches, dizziness, tremor, anxiety, confusion, dyspnoea, tachycardia, hypertension and increased sweating.
Intravenous injection of methylthioninium chloride has in some cases caused hypotension and cardiac arrhythmia, and in rare cases these problems can be fatal.

3.3. Conclusion
The efficacy and safety of methylene blue has been established using a literature review of 58 articles, published between 1935 and 2010 (three non-comparative clinical studies, one survey of poison centres, and 54 clinical cases).

In these studies, IV administration of methylene blue reduced methaemoglobin levels in patients with methaemoglobinaemia caused by chemical products or medicines.
The quality of the available data (open-label, non-comparative studies involving small numbers, lack of statistical tests, etc.) means that it is difficult to interpret the results.
No studies versus active comparators (e.g. ascorbic acid, n-acetylcysteins, tocopherol) are available.

According to the SPC, the most commonly observed adverse events are: nausea, abdominal and chest pain, headaches, dizziness, tremor, anxiety, confusion, dyspnoea, tachycardia, hypertension and increased sweating.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Methaemoglobinaemia caused by medicines or chemical products are medical emergencies which can in some cases be life-threatening, particularly in cases of severe poisoning (methaemoglobinaemia >70%).

This proprietary medicinal product is intended to provide curative treatment.

It is a first-line treatment.

The efficacy/adverse effects ratio is high.

> *Public Health Benefit:*
> Methaemoglobinaemia in adults and children is a serious toxic or congenital condition that can be life-threatening in cases of acute methaemoglobinaemia when the methaemoglobin level reaches 70%, but which is not a heavy public health burden because it is rare in France.
> Improved management of methaemoglobinaemia is a public health need that falls within the scope of identified priorities (Rare diseases plan 2010-2014).
> As a substitute for methylene blue, which is indispensable but which was available previously, PROVEBLUE METHYLTHIONINIUM CHLORIDE is not likely to have an additional impact on morbidity and mortality.
> It is not therefore expected to provide an additional response to an identified public health need.
> It is also not expected to have an impact on the healthcare system.
> Consequently, PROVEBLUE METHYLTHIONINIUM CHLORIDE is not expected to benefit public health.

The actual benefit of this proprietary medicinal product for this indication is substantial.

4.2. Improvement in actual benefit (IAB)

PROVEBLUE METHYLTHIONINIUM CHLORIDE is intended to replace AGUETTANT methylene blue. It is essential in the management of methaemoglobinaemia caused by medicines or chemical products. In this respect, the Transparency Committee considers that it maintains the significant therapeutic contribution that was made by AGUETTANT methylene blue.

4.3. Therapeutic use[4,5,6]

Methaemoglobin is the oxidised version (in the form of ferric iron) of haemoglobin, which does not bind oxygen. In normal physiology, methaemoglobin forms less than 1% of total haemoglobin.

Methaemoglobinaemia is the level of methaemoglobin in the blood; levels of over 3% are pathological. Symptoms (cyanosis, lethargy, headaches, caused by tissue hypoxia) start to appear when levels reach 8-10%. When levels reach 30% or above, the clinical presentation consists of slate-grey cyanosis which is not corrected with oxygen therapy and signs of respiratory, circulatory and neuropsychological distress; if levels are higher than 70%, poisoning can be fatal.

4 Orphanet
5 Methaemoglobinaemia caused by poisoning with poppers. Urgence on line, November 2010.
6 Bradberry SR et al. Occupational Methemoglobinemia Toxicol revue 2003; 33: 13-27.

Methaemoglobinaemia can be congenital, in most cases due to a deficiency in the cytochrome b5 reductase enzyme, but in the majority of cases it is an acquired condition caused by the ingestion of oxidising agents:

- chemical substances: nitrates and pesticides;
- some medicines: antibiotics, anaesthetics, quinine derivatives, etc.

In France, one of the most common causes of methaemoglobinaemia is inhalation or ingestion of poppers.

Treatment is based on administration of methylene blue and oxygen therapy.
Ascorbic acid can be sufficient to reduce cyanosis in mild cases; it is offered as a sole treatment, although reaction to it is slower, or in combination with methylene blue.
N-acetylcysteine and tocopherol can be offered in combination with or as an alternative to methylene blue, but their efficacy has not been confirmed.

Exchange transfusion can also be used in the most severe cases (MetHb > 50-70%) and/or if there is shock with severe intravascular haemolysis.

4.4. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services in the indication and at the dosages in the Marketing Authorisation.

APPENDIX 1

Results of a survey of poison centres in the European Community

Member states	Total number of cases	Cause of poisoning (number of cases)	Antidote used (manufacturer)	Protocol for treatment with MB
Austria	5 cases since 2003	- Sodium chlorate (3) - Gyromitra esculenta (false morel) (1) - Hydrogen sulfide (5)	Methylthioninium chloride 1% (pharmacy-compounded preparation)	1-2 mg/kg given by slow IV infusion
Belgium	69 cases since 1972: 40 adults 20 children (and 9 animals)	- Phenazopyridine (12) - Nitrites (11) - Chlorate (5) - Paracetamol (5) - Dapsone (4) - Loperamide (3) - Nitrates (3) - Substral (3) - Nitrobenzene (2) - Pyrimethamine (2) - Aniline (1) - Calorimeter (1) - Cocaine (1) - Dextromethorphan (1) - Chervil soup (1) - Linuron (1) - Metamizole (1) - Methylthioninium chloride (1) - organic nitrite (1) - Oxyphenbutazone (1) - Phenyl sulfone (1) - Beets (1) - Toluidine (1) - Tributylnitrite (1) - unknown (5)	Methylthioninium chloride 10 mg/mL (Sterop)	Adults and children: 1-2 mg/kg IV over 5-10 minutes. Repeat dose can be given after one hour if required.
Czech Republic	32 cases since 2004	- gentian violet (22)	Ascorbic acid only	Adults and children: 1-2 mg/kg (1% solution) over 5 minutes. Repeat dose after 30-60 minutes if patient does not respond
		- Aniline (5)	1 case: Toluidine blue (unknown) 4 cases: no treatment	
		- Dapsone (2)	Not specified	
		- Ortho-toluidine (1)	Not specified	
		- Isobutyl nitrite (poppers) (2)	1 case: Toluidine blue (unknown)	
Estonia	no cases since September 2008	Not available	Methylthioninium chloride (unknown)	1-2 mg/kg IV. Repeat dose can be given if required.
Finland	Not available	Not available	Methylthioninium chloride (unknown, compassionate use)	Not specified
France	Average of one case per year	- Poppers (amyl nitrite) - Chlorate - some anaesthetics	Methylthioninium chloride (unknown)	1-2 mg/kg IV maximum dose: 5-7 mg/kg.
Hungary	No information in the database			
Liechtenstein/ Switzerland	13 cases since 1997	- amyl nitrite (2) - Dapsone (2) - isopropyl nitrite (1) - isobutyl nitrite (1) - nitrite compound (1) - combustion (1) - kohl rabi (1) - Chloroaniline (1) - 4-bromo-2-fluoroaniline (1) - primaquine (1) - Unknown (1)	7 cases: Methylthioninium chloride for 7 cases (unknown) 6 cases: no treatment	1-2 mg/kg administered slowly via intravenous route, may be repeated up to a maximum of 7 mg/kg. Note: no reported side-effects or serious side-effects caused by MB

Member states	Total number of cases	Cause of poisoning (number of cases)	Antidote used (manufacturer)	Protocol for treatment with MB
Norway	2 cases in adults since 16 Feb 2004	- Unknown product containing nitrites (1) - unknown (1)	Metytionin injektionsvätska inj. 10 mg/mL (injectable product from Sweden)	Adults and children: 1-2 mg/kg slowly via intravenous route for 5 min. Repeat dose may be given after 1-4 h if required. Maximum total dose: 5-7 mg/kg.
Slovak Republic	2 cases since 2004	- nitrates in water (1) - aniline (1)	Toluidinblau (Dr. F. Kohler, Chemistry)	No MB available in the country
Spain	12 cases since May 2005	- linuron - naphthalene - phenazopyridine - pendimethalin (dinitroaniline herbicide)	methylthioninium chloride 1% in a 5% glucose solution (pharmacist-compounded preparation)	1-2 mg/kg IV over 5 minutes. Repeat dose can be given after one hour. Maximum dose: 7 mg/kg
Sweden	Fewer than 10 cases per year	Not stated	Methylthionine manufactured for National Use	Not stated
Netherlands	14 cases between 1 Jan 2007 and 31 Dec 2008	- cigarette containing firework powder (1) - aniline and P-aminoazobenzene (1) - resorcinol (1) - dapsone (2) - ammonium nitrates (1) - hydrogen peroxide 3% and phenacetin (1) - Isosorbide mononitrate (1) - nitrites and beer (1) - prednisolone and plaquenil (1) - nitrogen phosphate and potassium (1) - nitrites and cocaine (1) - methylthioninium chloride (2)	- Methylthioninium chloride (10 mg/mL) Alternative to MB: - Tolonium - Vitamin C (but less effective than MB)	Adults and children: 1-2 mg/kg IV over 5 minutes. A repeat dose may be given. Maximum dose: 7 mg/kg.

APPENDIX 2

Table 1: Clinical cases showing efficacy in adults with drug-induced methaemoglobinaemia

Reference	Cause	Patient	MB treatment	Route	Results
Cause: Chlorate and bromate local anaesthetics					
Young 2008	Oral Benzocaine spray	Man aged 27	65 mg (1-2 mg/kg)	IV	Complete recovery
Jiminez 2007	Hurricane spray (Benzocaine)	Woman aged 56	60 mg (1 mg/kg) over 5 min	IV	Cyanosis completely resolved in the minutes following MB administration
Kane 2007	Benzocaine	18 patients (mean age: 62.8 ± 16.0 years)	Mean dose ± SD: 1.3 ± 0.4 mg/kg body weight (range 0.7-2 mg/kg) 2nd dose required for 2 patients (after initial dose of 50mg)	IV	Signs and symptoms resolved in 1 hour (in most cases in 20-30 minutes)
Birchem 2005	Benzocaine	Woman aged 69	2 mg/kg	IV	1 hour later, MetHb levels reduced to 18.4% with improvement in cyanosis. 2 hours later, MetHb = 4%
Ash-Bernal 2004	Benzocaine	Man aged 52	Not stated	IV	Rapid reduction in methaemoglobinaemia
Sachdeva 2003	Benzocaine	Case 1: Man aged 72 Case 2: Man aged 65	Case 1: 2 mg/kg Case 2: 1 mg/kg	IV	Case 1: Cyanosis resolved and MetHb level fell within 2 hours Case 2: Cyanosis resolved within 15 minutes
Nguyen 2000	Benzocaine	Woman aged 71	1 mg/kg (1% solution) over 5 min	IV	Reduction in MetHb from 22.5% to 2.4% 1 hour after administration. Complete recovery.
Jaffery 2008	Topical benzocaine	Woman aged 44	2 mg/kg	IV	Symptoms resolved
Lin 2007	Topical benzocaine	Woman aged 29	50 mg over 10 minutes (1% solution)	IV	Reduction in MetHb levels
Saha 2006	Topical benzocaine	Man aged 71	1 mg/kg over 5 min	IV	Reduction in MetHb levels within 4 hours
Bayard 2004	Topical benzocaine	Woman aged 26	90 mg (2 mg/kg) over 5 min	IV	3 hours later: MetHb levels near zero.
Rodriguez 1994	Benzocaine	Man aged 83	100 mg (approx. 1.5 mg/kg) 2nd dose 3 hours later: 80 mg (1.1 mg/kg) 3rd dose 20 hours later: 80mg	IV	Reduction in MetHb concentration (from 54.1% to 4.3% after the 2nd dose). After the 3rd dose: reduction in MetHb from 30% to 4.2% in 4 hours
Bolyston 2002	Probably Benzocaine	Woman aged 73	200 mg in 100 mL of isotonic sodium chloride solution, infused over 30 minutes	IV	30 mins after infusion: MetHb level 9% 90 mins after infusion: MetHb level 2% Methaemoglobinaemia resolved rapidly
Wolak 2005	Multiple exposure to oxidising agents (mafenide acetate and benzocaine spray)	Man aged 21	2 mg/kg over 5 min Repeat dose 1 mg/kg	IV	Recovery
Adams 2007	Prilocaine	Woman aged 45	43 mg	IV	Rapid improvement
Wilburn-Goo 1999	Prilocaine	Case 1: Woman aged 22 Case 2: Woman	Case 1: 100 mg Case 2: unspecified dose, treatment over	IV	Case 1: complete recovery Case 2: MetHb level reduced to 2% in 5 mins

Reference	Cause	Patient	MB treatment	Route	Results
		aged 33 Case 3: woman aged 19	5 minutes Case 3: 1.5 mg/kg		Case 3: Recovery
Lunenfeld 2004	Topical anaesthetics (Cetacaine)	Man aged 52	1st dose: 1 mg/kg 2nd dose: 1 mg/kg, 5 mins after the 1st dose	IV	Complete recovery
Douglas 1977	Topical anaesthetic spray (Cetacaine)	Case 1: man aged 77 Case 2: woman aged 80	Case 1: 60 mg (6 mL of a 1% solution) with 250 mg of ascorbic acid Case 2: 50 mg (5 mL of a 1% solution)	IV	Case 1: Cyanosis resolved in 10 mins Case 2: Cyanosis resolved in a few mins
Cause: Antibiotics					
Arrivabene Caruy 2007	Dapsone	Man aged 52	1 mg/kg	IV	Clinical improvement 15 mins after administration
Matisoff 2006	Dapsone	Woman aged 71	1st dose: 5 mL (1% solution) Then further 5 mL doses (1% solution) up to a total of 20 mL	IV	Reduction in MetHb to 1.9%
Salamat 2003	Dapsone	Man aged 66	1 mg/kg over 10 min	IV	Rapid improvement in symptoms
Cause: amyl nitrite					
Modarai 2002	amyl nitrite	Case 1: woman aged 32 Case 2: man aged 28	Case 1: 1.5 mg/kg over 5 mins Case 2: 2 mg/kg over 5 mins	IV	Case 1: Improvement over 40 mins Case 2: Improvement over 10 mins
Stambach 1997	amyl nitrite	A woman aged around twenty	1st dose: 2 mg/kg 2nd dose: 1 mg/kg	IV	Complete recovery
Other causes					
Fung 2008	Ingestion of Zopiclone	Woman aged 43	1st dose: 80 mg (1 mg/kg) 2nd dose 90 mins later: 80 mg (1 mg/kg)	IV	Reduction in MetHb from 23.8% to 3.6% 1 hour after the 2nd dose Complete resolution of cyanosis
Mary 2000	Metoclopramide	Man aged 88	100 mg in 100 mL of normal saline solution administered over 3 mins	IV	Clinical improvement, MetHb levels returned to normal within 24 hours

Table 2: Clinical cases showing efficacy in children with drug-induced methaemoglobinaemia

Reference	Cause	Patient	MB treatment	Route	Results
Cause: Chlorate and bromate anaesthetics					
Autret 1989	Nestosyl	Girl aged 2 years	1 mg/kg (MB 1%)	IV 5 min	Cyanosis resolved and O_2 and PaO_2 saturation normal 15 mins after MB administration.
Dahshan 2006	Topical benzocaine spray	Children aged 3 years	1 mg/kg	IV	MB rapidly resolved central cyanosis, restored normal oxygen saturation, and improved arterial blood gases
Hersch 2004	Exposure to benzocaine	Case 1: 2.5 years Case 2: 5.5 years	Case 1: 10 mg Case 2: 20 mg	IV	Case 1: Cyanosis visibly reduced within 8 mins, with MetHb levels reduced to 4.4% within 6 hours Case 2: Cyanosis resolved in 15 mins
Tush 1996	Benzocaine and resorcinol (Vagisil) cream (OTC	Newborn aged 6 days	3 mg (1 mg/kg)	IV	Skin colour returned to normal 45 minutes after the dose

Reference	Cause	Patient	MB treatment	Route	Results
	medication)				
Fullerton 2002	Mafenide acetate 5% solution and topical lidocaine spray	Boy aged 12 years	0.1 mL/kg (1% solution) over 5 minutes	IV	Breathing and cyanosis improved rapidly after MB infusion. MetHb at 2 hours and 12 hours after treatment was 4.1% and 2.5% respectively.
Guay 2009	Benzocaine	Review of 242 cases (adults and children)	MB (n=155) or MB plus ascorbic acid (n=14), 1st dose of MB between 0.5 and 5.5 mg/kg Cumulative MB dose: between 0.6 and 9.4 mg/kg	IV	In patients who received MB +/- ascorbic acid: - Time until MetHb fell to ≤ 2.0% was between 0.33 and 36.2 hours. - Time until clinical cyanosis resolved: between 0.25 and 9 hours In one day-old newborn who received a single dose of 1.0 mg/kg MB: haemolysis, attributed to administration of MB
Ozdogan 2010	Prilocaine	Infant aged 40 days	1 mg/kg	IV	Cyanosis resolved in 60 minutes. MetHb level reduced to 4% in 60 minutes and to 1.5% in 24 hours. Cyanosis resolved completely after 120 minutes.
Bouziri 2010	Skin application of an ointment containing benzocaine, resorcinol and oxyquinoline (Nestosyl)	Boy aged 16 months	Loading dose: 2 mg/kg 1% MB solution followed by 1 mg/kg twice daily	Slow IV infusion 5 min	Rapid improvement in cyanosis and in neurological and haemodynamic status. 24 hours later, MetHb had reduced from 50.6% to 9.8%. Patient discharged on day 3.
Cause: Antibiotics					
Ferguson 1997	Intentional poisoning with dapsone	Girl aged 14 years	1st dose: 90 mg total dose over 48 hours: 8 mg/kg	Bolus IV infusion	1 hour after the 1st dose, MetHb level: 5.9% but MetHb level rapidly increased (to over 25%). MetHb reduced over the following 4-5 days, after total MB dose of 8 mg/mL.
MacDonald 1997	Acute dapsone poisoning	Boy aged 3 years	4 doses of 16 mg (1% solution, 0.1 mg/kg) with activated charcoal	IV	3 doses of MB reduced MetHb level to 6%
Tsai 2005	Sulfadiazine	3 years	1 mg/kg	IV	Reduction of MetHb to 1% in 1 hour
Moodambail 2005	Dapsone	Child aged 19 months	1 mg/kg MB 1%. diluted in distilled water, 2nd dose given 10 hours after the 1st Cumulative MB dose: 2 mg/kg	Slow IV infusion over 10 mins	MetHb fell after 10 hours from 28.1% to 21%. Cyanosis improved spectacularly. After the 2nd dose: MetHb levels insignificant for the following 2 days, and patient went home.
Other causes					
Merieau 2005	Metoclopramide	Newborn aged 5 days	1 mg/kg	IV	Cyanosis resolved within 1 hour. MetHb level fell from 11.2% to 0.4%.
Attof 2006	Cerium nitrate (topical antiseptic)	Girl aged 16 years	1.5 mg/kg (i.e. 100 mg) over 15 mins	Not stated	MetHb fell from 31.8% to 3.5% 1 hour after treatment
Se Eun Hyun 2009	Chinese herbal medicine	Girl aged 8 years	2 mg/kg of MB 1%. Treatment was repeated on day 2 Cumulative MB dose: 4 mg/kg	IV Inf.	After 1st dose: MetHb fell to 13.1%, cyanosis and dyspnoea improved. After 2nd dose: MetHb fell to 2.5% and 1.3% on admission days 3 and 4 respectively. Patient sent home on day 6.

Table 3: Clinical cases showing efficacy in adults with methaemoglobinaemia caused by a chemical product

Reference	Cause	Patient	MB treatment	Route	Results
Cause: Aniline products					
Demirel 1999	Aniline	Case 1: man aged 54 Case 2: man aged 37	Case 1: 140 mg Case 2: 150 mg	IV	Case 1: Reduction of MetHb to 4.9% in 1 hour. Fell to 1.5% after several hours Case 2: Reduction of MetHb to 7.5% in 2 hours Completely resolved.
Ferrer-Gomez 2008	Aniline	Man aged 19	1st dose: 80 mg over 10 mins 2nd dose: 1 mg/kg 3rd dose: not stated Total dose: 3 mg/kg	IV	Improvement
Kearney 1984	Aniline	Man aged 32	- 200 mg (plus 500 mg ascorbic acid) - 2nd dose: 300 mg (plus 1 g ascorbic acid) - over the following 12 hours: 800 mg (plus 2.5 g ascorbic acid) in 5 doses - 20 hours after poisoning, 180 mg	IV	MetHb fell from 70% to 24%. MetHb level subsequently fell spontaneously. Patient was directed towards quantitative G6PD testing but was lost to follow-up.
Mullick 2007	Aniline in a patient with G6PD deficiency	Woman aged 23	50 mg (1% solution) in normal saline solution for 10 minutes	IV	No clinical improvement 1 hour later, because of G6PD deficiency. Oxygen therapy was used.
Harvey 1983	Aniline	Man aged 22	- 1st dose: 150 mg (2 mg/kg) - 2nd dose: 150 mg	IV	Reduction in MetHb levels
Liao 2002	Aniline	Man aged 25	40 mg	IV	Clinical improvement, but a G6PD deficiency was identified
Pizon 2009	*p*-chloroaniline	Man aged 20	2 mg/kg	IV	Complete recovery
Cause: Other chemical products					
Anic 1999	Herbicide "Galex 500 EC" (25% metolachlor and 25% metobromuron dissolved in xylene)	Man aged 81	1.5 mg/kg (10 mL, 1% solution)	IV	Very effective, complete recovery
Geiger 1935	Cyanide poisoning	Woman aged 28	1st dose: 50 cm^3 (1% solution) 2nd dose (50 cm^3 1% solution) administered 10 minutes after the 1st dose	IV	8 minutes after the 1st injection, respiratory function was restored. Definitive improvement obtained 30 minutes after the 2nd dose.
Maric 2008	Food additive	4 patients (age not stated)	Not stated	IV	Rapid clinical improvement

Table 4: Clinical cases showing efficacy in children with methaemoglobinaemia caused by a chemical product

Reference	Cause	Patient	MB treatment	Route	Results
Cause: Aniline					
Maione 1990	Aniline (shoe dye)	15 years	2 mg/kg	IV	After administration, MetHb level in Hb fell, and level of consciousness improved immediately.
Hjelt 1995	Toxic substance (probably para-chloraniline)	premature infants (n=13)	28 doses of MB: - 0.1-0.2 mg/kg body weight (n=7) - 0.3-0.9 mg/kg body weight (n=10) - 1.0-1.6 mg/kg body weight (n=11)	IV	Treatment for severe methaemoglobinaemia in premature infants using 0.3-1.0 mg/kg proved to be effective. One of the possible side-effects is an increased need for transfusion. The lowest effective dose of MB must therefore be used.
Golden 1998	Ingestion of fluid for removal of false fingernails, which contained nitroethane.	Boy aged 26 months	2 administrations of 2 mg/kg MB over 14 hours Cumulative MB dose: 4 mg/kg	IV	MB failed to reduce MetHb, because of G6PD deficiency.
Savino 2006	High concentration in courgette soup (nitrates)	Infant aged 2 months Infant aged 1 month	0.1 ml/kg (1% solution)	Not stated	Symptoms completely resolved after 12 hours