

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Pentostam Injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Sodium Stibogluconate equivalent to 100 mg pentavalent antimony in each ml.

3 PHARMACEUTICAL FORM

Injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Pentostam should be used in accordance with international and local treatment guidelines. Consideration should be given to visceral leishmaniasis resistance patterns prior to administration.

Pentostam is indicated for the following diseases:

Visceral leishmaniasis (kala azar).

Cutaneous leishmaniasis.

South American mucocutaneous leishmaniasis.

Pentostam may also be of value in the treatment of leishmaniasis recidivans and diffuse cutaneous leishmaniasis in the New World.

NOTE:-

- There is limited data available on the effectiveness of sodium stibogluconate to treat cutaneous and diffuse cutaneous leishmaniasis caused by *Leishmania infantum* and *Leishmania aethiopia*.

4.2 Posology and method of administration

Route of administration

Due to the presence of particulates (size range 20 to 300 microns) Pentostam solution should be drawn up through a filter immediately prior to administration. These particulates are insoluble complexes formed by an interaction between product preservative and the antioxidant in the rubber stopper. Filters of pore size 5 micron or less and membrane types polyvinylidene difluoride, polyethersulphone, polysulphone, nylon, surfactant-free cellulose acetate and mixed cellulose esters have been shown to be suitable. Where sterile filters are not available the risks and benefits of administering unfiltered Pentostam therapy should be assessed by the clinician on an individual basis.

All dosage recommendations are based on the findings of the WHO Expert Committee on leishmaniasis which met in 2010. There are no special recommendations for different age groups.

Visceral leishmaniasis: 20 mg pentavalent antimony (0.2 ml Pentostam) per kg bodyweight daily intramuscularly or intravenously for 30 days (or 28 days for *L. infantum*). Patients should be examined for evidence of relapse after 2 and 6 months and in Africa after 12 months.

Cutaneous leishmaniasis caused by Old World species:

- For lesions requiring local therapy
 - 100-500mg intralesional pentavalent antimony (1-5mL sodium stibogluconate injection) per session every 3-7 days for 1-5 sessions.
- For lesions requiring systemic therapy
 - 20mg/kg pentavalent antimony (0.2 mL sodium stibogluconate injection) intramuscularly or intravenously for 10-20 days.

Monotherapy with sodium stibogluconate is not recommended for the treatment of cutaneous leishmaniasis caused by *L. aethiopica*. Please refer to WHO treatment recommendations for leishmaniasis.

Cutaneous leishmaniasis caused by New World species:

- For lesions requiring local therapy
 - 100mg-500mg intralesional pentavalent antimony (1-5mL sodium stibogluconate injection) per session every 3-7 days for 1-5 sessions.
- For lesions requiring systemic therapy
 - 20mg/kg pentavalent antimony (0.2mL sodium stibogluconate injection) intramuscularly or intravenously for 20 days.

Monotherapy with sodium stibogluconate is not recommended for relapse treatment. Please refer to WHO treatment recommendations for leishmaniasis.

Muco-cutaneous leishmaniasis: Patients should be treated with 20 mg Pentavalent antimony (0.2 ml Pentostam) per kg bodyweight daily intramuscularly or intravenously for 30 days.

Little data are available for the therapy of MCL due to *L. aethiopica*.

Diffuse cutaneous leishmaniasis in the New World and leishmaniasis recidivans: For diffuse cutaneous leishmaniasis in the New World and leishmaniasis recidivans combination therapy should be considered. Please refer to WHO treatment recommendations for leishmaniasis.

Use in the elderly: There is little information on the effects of Pentostam on elderly individuals. If treatment of cutaneous leishmaniasis is necessary then local infiltration is preferred. The normal precautions should be strictly adhered to when treating older patients for visceral leishmaniasis.

4.3 Contraindications

Pentostam should not be given to any patient with significantly impaired renal function.

Pentostam should not be given to any patient who has experienced a serious adverse reaction to a previous dose.

4.4 Special warnings and precautions for use

Intravenous injection should be filtered immediately before use (see Posology and Method of Administration). Administer very slowly over 5 minutes to reduce the risk of local thrombosis. In the unlikely event of coughing, vomiting or substernal pain occurring, administration should be discontinued immediately. In such cases, extreme care should be taken if Pentostam is re-administered by this route.

Successful treatment of mucocutaneous leishmaniasis may induce severe inflammation around the lesion. In cases of pharyngeal or tracheal involvement, this may be life-threatening. Under such circumstances, corticosteroids may be used.

Very rarely, anaphylactic shock may develop during treatment for which adrenaline injection and appropriate supportive measures should be given immediately.

Prolongation of the QTc interval has been observed in some patients taking sodium stibogluconate and appears to be dose-related. There have also been reports of fatal cardiac arrhythmias in patients receiving higher dose antimonial therapy for visceral leishmaniasis. Therefore, ECG monitoring is recommended before and during therapy with sodium stibogluconate. Where ECG monitoring is not available, the risks and benefits of sodium stibogluconate therapy should be assessed on an individual basis.

If clinically significant prolongation of QTc interval occurs, sodium stibogluconate should be discontinued. Electrocardiographic changes, notably alterations in T wave amplitude may be expected in the majority of patients

given sodium stibogluconate, these appear to be reversible on cessation of therapy and are not of serious significance.

Sodium stibogluconate should be used with caution in patients with cardiovascular disease, a history of ventricular arrhythmias or other risk factors known to predispose towards QT prolongation: for example, those with congenital QTc prolongation or taking concomitant drugs known to significantly prolong the QT interval (e.g. class III anti-arrhythmics such as sotalol and amiodarone).

As there appears to be a dose relationship in the development of ECG abnormalities, prior exposure to antimonial therapy should be considered when assessing a patient's suitability for initiating or continuing therapy with sodium stibogluconate.

Patients who have recently received other antimonial drugs should be monitored closely for signs of antimony intoxication such as bradycardia and cardiac arrhythmias during administration of sodium stibogluconate.

There have been some reports of cardiac arrhythmias and sudden death when amphotericin B deoxycholate is administered soon after sodium stibogluconate for retreatment of visceral leishmaniasis. Allowing a resting period of 14 days between sodium stibogluconate treatment and starting amphotericin B deoxycholate may reduce this risk. Electrolyte imbalances should be corrected prior to administration of amphotericin B deoxycholate with close monitoring of patients (see section 4.5).

Intercurrent infections, such as pneumonia, should be sought and treated concomitantly.

High concentrations of antimony are found in the livers of animals after repeated dosage with pentavalent antimony. Pentostam should therefore be used with caution in patients with hepatic disease. However, some abnormalities of liver function may be expected in cases of visceral leishmaniasis. In such patients the benefit of pentavalent antimony treatment outweighs the risk. Pentostam may induce mild elevation of hepatic enzymes in serum which later return to normal.

The Pack for this product carries the following statements:

Keep out of the reach and sight of children

Do not store above 25°C. Do not freeze.

Protect from light

Poison

In addition the 100 ml pack will have the following statement:

The contents should not be used more than 1 month after removing the first dose.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions with Pentostam have been reported.

An increased risk of fatal cardiac arrhythmias has been observed when amphotericin B deoxycholate is administered soon after sodium stibogluconate during retreatment of visceral leishmaniasis. Although the mechanism is unknown it is suggested that sodium stibogluconate increases the susceptibility of the myocardium to damage by amphotericin B deoxycholate (see section 4.4).

4.6 Pregnancy and lactation

Although no effects on the foetus have been reported, Pentostam should be withheld during pregnancy unless the potential benefits to the patient outweigh the possible risk to the foetus.

Children should not be breast-fed by mothers receiving Pentostam.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Approximately 1 to 2% of patients complain of nausea, vomiting and/or diarrhoea and a slightly higher number of abdominal pain.

Other common side-effects include anorexia, malaise, myalgia, arthralgia, headache and lethargy.

ECG changes, including reduction in T-wave amplitude, T-wave inversion and QT prolongation have been observed (see Section 4.4 Special Warnings and Precautions for Use).

Transient coughing immediately following injection was reported with varying frequency during several trials.

Intravenous injection of Pentostam may cause transient pain along the course of the vein and eventually thrombosis of that vein.

Transient rises in serum lipase and amylase usually occur during treatment with sodium stibogluconate. Symptomatic pancreatitis has also been reported.

During some early trials of sodium stibogluconate, pneumonia occurred in a small number of patients treated for visceral leishmaniasis and this occasionally proved fatal. Pneumonia is a feature of the visceral leishmaniasis disease process; however, it has been associated with the toxicity profile of trivalent antimony. It is, therefore, not possible to determine whether these cases were due to the disease or to Pentostam.

Other (rarely reported) side-effects include fever, rigor, sweating, vertigo, facial flushing, worsening of lesions on the cheek, bleeding from the nose or gum, substernal pain, jaundice and rash.

Transient reductions in platelets, white blood cells and haemoglobin.

4.9 Overdose

The main symptoms of antimony overdosage are gastro-intestinal disturbances (nausea, vomiting and severe diarrhoea). Haemorrhagic nephritis and hepatitis may also occur.

There is only limited information on the use of chelating agents in the treatment of intoxication with antimony compounds. Dimercaprol has been reported to be effective: a dose of 200 mg by intramuscular injection, every six hours until recovery is complete, is suggested.

2,3-dimercaptosuccinic acid (DMSA) may also be effective treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The mode of action of Pentostam is unknown. *In vitro* exposure of amastigotes to 500 mg Sb⁵⁺/ml results in a greater than 50% decrease in parasite DNA, RNA protein and purine nucleoside triphosphate levels. It has been postulated that the reduction in ATP (adenosine triphosphate) and GTP (guanosine triphosphate) synthesis contributes to decreased macromolecular synthesis.

5.2 Pharmacokinetic Properties

Following intravenous or intramuscular administration of sodium stibogluconate, antimony is excreted rapidly via the kidneys, the majority of the dose being detected in the first 12-hour urine collection. This rapid excretion is reflected by a marked fall in serum or whole blood antimony

levels to approximately 1 to 4% of the peak level by 8 hours after an intravenous dose. During daily administration, there is a slow accumulation of sodium stibogluconate into the central compartment so that tissue concentrations reach a theoretical maximum level after at least 7 days.

5.3 Preclinical Safety Data

There are no preclinical data of relevance to the prescriber which are additional to that in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Chlorocresol BP
Glucono-delta-lactone HSE
Water for Injections EP

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months.

Not to be used more than 1 month after removing the first dose. Once opened, do not store above 25°C, do not freeze and protect from light.

6.4 Special precautions for storage

Do not store above 25°C. Do not freeze.
Protect from light.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and Contents of Container

Amber glass vials sealed with synthetic butyl rubber closures and aluminium collars.

Pack sizes: 6 and 100 ml.

6.6 Instruction for Use/Handling

Pentostam solution should be filtered immediately prior to use (see Posology and Method of Administration).

7 MARKETING AUTHORISATION HOLDER

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