SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<TRADE NAME> <STRENGTH> Solution for Injection

<REGARDING THE APPROVAL>

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains <STRENGTH> of thiamine hydrochloride.

Excipient with known effect:

<REGARDING THE APPROVAL>

For the full list of excipients, see section 6.1.

1. PHARMACEUTICAL FORM

Solution for Injection

<REGARDING THE APPROVAL>

1. CLINICAL PARTICULARS
   1. Therapeutic indications

Thiamine hydrochloride is indicated for the prevention and the treatment of vitamin B1 deficiencies like beriberi, deficiency related to chronic alcoholism and Wernicke-Korsakoff syndrome.

* 1. Posology and method of administration

Posology

Adults

* Beriberi:
* Treatment: 10 mg – 20 mg by intramuscular injection or slow intravenous infusion (over 30 minutes) 3 times/day for up to 2 weeks.

If severe life threatening form of beriberi (e.g. shoshin beriberi): 100 mg to 300 mg/day by slow intravenous infusion.

* Maintenance treatment: the treatment should be continued with an adapted oral form of vitamin B1.
* Wernicke-Korsakoff syndrome associated with alcohol use disorder:
* Prophylaxis in patients with high risk (e.g. hospitalized patients managed for alcohol withdrawal in presence of malnutrition): 250 mg by intramuscular or intravenous route 1 time/day for 3 to 5 days.
* Treatment: 500 mg to 750 mg by intravenous route 3 times/day for at least 2 days (up to 1000 mg/dose during the first 12 hours may be used). In case of favorable response the treatment can be continued with 250 mg by intramuscular or intravenous route 1 time/day for 5 days or until there is no further improvement.
* Maintenance treatment: the treatment should be continued with an adapted oral form of vitamin B1.

Patients with marginal thiamine status to whom glucose is being administered should receive 100 mg thiamine hydrochloride in each of the first few liters of IV fluid to avoid precipitating heart failure (see section 4.4).

Paediatric population

There is only limited experience with therapy in children and adolescents.

* Beriberi:
* Treatment: 10 mg to 25 mg/day by intramuscular injection or slow intravenous infusion for 2 weeks.

IV doses of 100 mg/day or even higher may be needed in severe cases, for example 500 mg three times a day could be used (see section 5.1).

* Maintenance treatment: the treatment should be continued with an adapted oral form of vitamin B1.

Elderly

There are no data available in the elderly. No dose adjustment is recommended for this population. Interactions with other medicines should be considered (see sections 4.5 and 5.2).

Renal impairment

The influence of renal impairment on the pharmacokinetics of thiamine has not been evaluated. No dose adjustment is recommended, but caution is advised when treating patients with renal impairment (see sections 4.4 and 5.2).

Hepatic impairment

The influence of hepatic impairment on the pharmacokinetics of thiamine has not been evaluated. No dose adjustment is recommended, but caution is advised when treating patients with hepatic impairment (see section 5.2).

Method of administration

Thiamine hydrochloride should be administrated by slow intravenous or intramuscular route.

**For slow intravenous administration, the drug solution must be first diluted into 50 ml to 250 ml of 5% glucose or 0.9% sodium chloride sterile solutions. The injection is administrated slowly over 30 minutes.**

For instructions on dilution of the medicinal product before administration, see section 6.6.

For intramuscular administration, use the undiluted drug solution. Deep intramuscular injection must be given into a big muscular mass (upper outer quadrant of the buttock or the lateral part of the thigh). Before injection of the dose, suck up to be sure that the needle is not into a vein. If blood appears, take the needle out and inject into another site. Change the injection site in case of repeated doses..

* 1. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

* 1. Special warnings and precautions for use

Warnings

* + Parenteral route must be used only when rapid restauration of thiamine is necessary (e.g. Wernicke-Korsakoff syndrome) or when oral route is ineffective (e.g. in case of vomiting, malabsorption).
  + The 50 mg/ml solution will be less painful when administered by IM route as it is much less hypertonic than the 125 mg/ml solution. Prefer the IV administration (after dilution) for the 125 mg/ml solution, especially for long-term treatment.
  + Anaphylactic reactions leading to shock have been reported after thiamine hydrochloride parenteral administration (see section 4.8).This risk increases in case of repeated doses. An intradermal test dose is recommended prior parenteral administration in patients suspected to be drug sensitive. Emergency medical equipment for treating anaphylactic shocks must be easily available.
  + To reduce the risk of anaphylactic shock and reactions at the injection site, the intravenous injection must be administered slowly (over 30 minutes). Fast IV administration of 100mg thiamine hydrochloride is associated with an immediate burning sensation in the arm after injection in the IV line, lasting seconds to minutes. This reaction can be avoided by slow administration into larger veins with higher IV fluid flow rates (see section 4.8).
  + As thiamine plays the role of enzymatic cofactor in the normal metabolism of glucides, an important intake of glucose quickly provokes a depletion of the reserves, and precipitates or aggravates a Wernicke encephalopathy in patients suffering from an underlying thiamine deficiency. It is consequently recommended to administer thiamine intravenously before or simultaneously with administration of glucose by bolus or by infusion (see sections 4.2 and 4.8).
  + Patients with renal impairment may need an extra careful monitoring (see sections 4.2 and 5.2).
  + This medicine contains less than 1 mmol sodium (23 mg) per 2 ml ampoule, that is to say essentially “sodium-free”. <REGARDING THE APPROVAL>

Precautions for use

* + Do not use this medicine if you notice visible particles in the solution, if the solution is not clear or if it contains a precipitate.
  + This drug solution and any syringe containing this medicine are destined for single and individual use (see section 6.3).

*Interference with laboratory tests*

Thiamine can give false positive results for urobilinogen determination by the Ehrlich's reaction (urine test) and for uric acid determination by the phosphotungstene method. High doses of thiamine may interfere with Schack and Waxler spectrophotometric assays of theophylline plasma concentration.

* 1. Interaction with other medicinal products and other forms of interaction

Medicines that may decrease the effect of thiamine

* + The thiamine antagonists: 5-fluorouracil, other fluoropyrimidines (e.g. capecitabine) and ifosfamide.
  + Diuretics, e.g. furosemide that may increase urinary thiamine excretion.

Thiamine deficiency can occur with the chronic use of these medicines. Consider high-dose thiamine supplementation during the treatment with these medicines.

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* 1. Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of thiamine in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). The use of the product is individualized based on condition and requirements in pregnant women and can be used in pregnant women if use is necessary to correct deficiencies and if benefits overweight risks.

Caution should be exercised when prescribing to pregnant women. The risk of anaphylactic reactions present during parenteral administration must be taken into account.

Breastfeeding

Thiamine is excreted in human milk. At recommended daily intake levels no effects on the breastfed newborns/infants are anticipated. However, there is insufficient information on the levels and possible effects of excretion of thiamine in human milk after administration of high levels of thiamine (> 50 mg/day). A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from thiamine therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

No relevant data is available.

* 1. Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. However, patients should be cautioned to see how they react before driving or operating machinery.

* 1. Undesirable effects

Adverse effects with thiamine are rare, but hypersensitivity reactions have occurred, mainly after parenteral administration. These reactions have ranged in severity from very mild to very rarely, fatal anaphylactic shock. Pain and an immediate burning sensation in the arm have been reported after a fast intravenous administration.

The possible side effects are listed below. The frequency of the possible side effects is defined as following:

* Very common (>1/10).
* Common (>1/100, <1/10).
* Uncommon (>1/1,000, <1/100).
* Rare (>1/10,000, <1/1,000).
* Very rare (<1/10,000).
* Unknown (cannot be estimated from the available data).

The side effects are presented by System Organ Class and in order of decreasing seriousness within each frequency category.

|  |  |  |
| --- | --- | --- |
| **Organ system** | **Underirable effect** | **Frequency** |
| Immune system disorders | Allergic or anaphylactic reactions (with respiratory depression, pruritus, shock and abdominal pain)1 | Unknown |
| Skin and subcutaneous tissue disorders | Contact dermatitis (which can appear after administration to sensitized individuals) | Unknown |
| General disorders and administration site conditions | Injection site reactions (pain, burning in the arm)2 | Unknown |

1Reaction observed after repeated injections of high doses from 25 mg to 100 mg thiamine hydrochloride, at intervals of more than 7 days. These reactions are frequently preceded by sneeze or transient pruritus. The risk of anaphylactic shock can be reduced by a slow administration over 30 minutes.

2Fast intravenous administration of 100 mg thiamine hydrochloride is associated with an immediate burning sensation in the arm after injection in the IV line, lasting seconds to minutes. This reaction can be avoided by a slow administration into larger veins with higher IV fluid flow rates (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Health Product Vigilance Center; HPVC

* 1. Overdose

Symptoms and signs

Thiamine is widely used, serious toxicity is not expected.

Single parenteral doses of 100 mg to 500 mg have been given with no toxic effects reported. Toxicity is uncommon following oral ingestion, excessive doses are usually excreted rapidly in the urine. Long-term ingestion of doses greater than 3000 mg daily has been known to produce toxicity.

Severe toxicity has not been reported.

Treatment

In the unlikely event of overdosage, treatment is symptomatic and supportive.

In case of mild or moderate anaphylaxis: antihistamines are given (with or without inhaled beta agonists), corticosteroids or epinephrine.

In case of severe anaphylaxis occurs: oxygen, airway management, antihistamines, epinephrine, corticosteroids, ECG monitoring, and IV fluids.

1. PHARMACOLOGICAL PROPERTIES
   1. Pharmacodynamic properties

Pharmacotherapeutic roup: vitamin B1 plain. ATC code: A11DA01

Mechanism of action

The principal physiological role of thiamine is as a coenzyme in carbohydrate metabolism, where thiamine pyrophosphate (TPP) is required for several stages in the breakdown of glucose to provide energy.

Thiamine combined with adenosine triphosphate (ATP) is converted to the active coenzyme thiamine pyrophosphate (thiamine diphosphate) by the enzyme thiamine diphosphokinase. Thiamine pyrophosphate is a coenzyme in carbohydrate metabolism (in the decarboxylation of pyruvic and alpha-ketoglutaric acids) and in transketolation reactions. Thiamine diphosphate is also a coenzyme in the utilisation of pentose in the hexose monophosphate shunt.

Pharmacodynamics

Thiamine deficiency results in beriberi and Wernicke-Korsakoff syndrome. Clinical signs of thiamine deficiency become evident after 2-3 weeks of inadequate thiamine intake. The organ systems principally affected by thiamine deficiency are the nervous system, cardiovascular system, and GI tract. Administration of thiamine completely reverses the cardiovascular and gastro-intestinal symptoms of thiamine deficiency. However the degree of improvement in neurologic symptoms depends on the duration and severity of the lesions.

Fatal deficiency can develop as rapidly as within 3-4 weeks in the absence of thiamine intake. Several cases of fatal, acute beriberi developing within 5 weeks in patients receiving thiaminedeficient total parenteral nutrition solutions have been observed.

Clinical efficacy and safety

In early stages of severe deficiencies like Wernicke-Korsakoff syndrome or Shoshin beriberi, parenteral administration of thiamine rapidly reverses the clinical symptoms. The improvement of symptoms is sufficient to make the diagnosis, even if serum thiamine measurement is not available.

In Wernicke-Korsakoff syndrome, early recognition and treatment is important, both because of the risk of collapse and sudden death, and to prevent irreversible damage to the CNS. Korsakoff symptoms respond less well to treatment than those associated with Wernicke's encephalopathy, and may indeed only become evident on treatment. This justifies the recommended high doses for the treatment (see section 4.2).

Thiamine has a well-established safety profile. The only adverse events observed with parenteral administration include injection site pain, contact dermatitis, and mild to anaphylactic allergic reactions. More of these events are easy to manage, though there have been reports of severe anaphylaxis following IV thiamine (see sections 4.4 and 4.8). In case of anaphylaxis administration of thiamine should be discontinued and standard anaphylaxis care should be initiated.

*Paediatric population*

In one case report, a 13 years old boy was treated with high doses of thiamine: 100 mg/day then 500 mg three times a day. The patient completely recovered after 20 days of replacement therapy (see section 4.2).

* 1. Pharmacokinetic properties

Absorption

Thiamine is rapidly and completely absorbed after intramuscular administration.

Distribution

In the plasma thiamine is nonspecifically bound to several proteins, especially albumin.

It is widely distributed to most body tissues. It is not known if thiamine crosses placenta. Supplementation did not significantly affect thiamine concentration in breast milk of healthy, well-nourished women and appears in breast milk in lactating women with poor nutritional status. The authors supposed that absorptive capacity of the mammary gland may be saturable. Within the cell, it is mostly present as diphosphate.

Thiamine is a water-soluble vitamin and therefore the quantity of thiamine reserves in the lipid structures of body cells is quite low, with the maximum storage capacity being 30 mg.

Biotransformation and elimination

In animals thiamine is metabolised in the liver. Several urinary metabolites of thiamine have been identified in humans. Little or no unchanged thiamine is excreted in urine following administration of physiologic doses; however, following administration of large doses, both unchanged thiamine and metabolites are excreted after tissue stores become saturated. In thiamine deficiency, thiamine is generally absent from the urine. However, a patient can be clinically (or subclinically) thiamine-deficient despite a “normal” serum and urinary thiamine excretion level.

Specific groups of patients

*Renal impairment*

The influence of renal impairment on the pharmacokinetics of thiamine has not been evaluated.

No data is available suggesting that dosing changes are necessary for patients with renal issues. Thus no dose adjustment is required in patients with renal impairment. But, as elimination through the urine is the main excretion pathway, it is conceivable that patients with disturbed urinary function may build up high systemic doses of thiamine and its metabolites. Though no knowledge nor proof on potential toxicity exists, given the anaphylactic potential of the compound, extra careful monitoring in these patients is advisable (see sections 4.2 and 4.4).

Dialysed patients are at high risk of being deficient in vitamin B1. These patients may also have a resistance to vitamin activity.

*Hepatic impairment*

The influence of hepatic impairment on the PK of thiamine has not been evaluated. No dose adjustment is required in patients with hepatic impairment but that caution is advised in these patients (see section 4.2).

*Effect of gender, race and weight*

The influence of gender, race and weight has not been established, and there are no data concerning the effect of these factors on the PK of thiamine.

*Elderly*

There are no pharmacokinetic data in the elderly. No dose adjustment is recommended for this population (see section 4.2).

*Paediatric population*

There is only limited experience with therapy in paediatric population (see section 4.2).

* 1. Preclinical safety data

There are insufficient data to exclude genotoxicity, carcinogenicity or reproductive toxicity. There are no other non-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SmPC.

1. PHARMACEUTICAL PARTICULARS
   1. List of excipients

<REGARDING THE APPROVAL>

* 1. Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

* 1. Shelf life

<REGARDING THE APPROVAL>

* 1. Special precautions for storage

<REGARDING THE APPROVAL>

* 1. Nature and contents of container

<REGARDING THE APPROVAL>

* 1. Special precautions for disposal

The solution should be inspected visually before use (and after dilution). Only clear solutions free from visible particles should be used.

Dilution for infusion

Thiamine HCl Sterop can be administered by slow intravenous injection after dilution in 50 ml to 250 ml of sterile glucose 50 mg/ml (5%) or sodium chloride 9 mg/ml (0.9%) solution for up to 8 hours without protection from light.

The solution after dilution remains clear, colourless to pale yellow and free from visible particles.

Any unused medicinal product, waste material or medicinal solution should be disposed of in accordance with local requirements.

<REGARDING THE APPROVAL>

1. MARKETING AUTHORISATION HOLDER

<REGARDING THE APPROVAL>

1. MARKETING AUTHORISATION NUMBER(S)

<REGARDING THE APPROVAL>

1. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<REGARDING THE APPROVAL>

1. DATE OF REVISION OF THE TEXT1

<REGARDING THE APPROVAL>