HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

29 May 2013

HYDRAPERF, infusion solution

B/1 bag of 500 ml (CIP: 34009 222 568 3 2)
B/20 bags of 500 ml (CIP: 34009 222 571 4 3)

Applicant: AGUETTANT

INN	Glucose monohydrate, sodium chloride
ATC Code (2012):	B05BB02 (blood substitutes and infusion solutions)
Reason for the request	**Inclusion**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17) for the box with 1 bag **Hospital use** (French Public Health Code L.5123-2) for boxes with 1 and 20 bags
Indications concerned	**"- Rehydration in case water loss is higher than sodium chloride and other osmoles loss** **- Prevention of intra- and extracellular dehydration** **-Vehicle for therapeutic supplementation when compensating for abundant diuresis without carbohydrate overload."**

Actual Benefit	**The actual benefit is substantial in the Marketing Authorisation indications.**
Improvement in Actual Benefit	**HYDRAPERF does not provide any improvement in actual benefit (IAB V, non-existent) compared to other infusion solutions containing glucose and/or sodium chloride used in particular for rehydration and for preventing dehydration.**
Therapeutic use	**HYDRAPERF is a first-line medicine.**
Recommendation	**The Committee recommends inclusion on the list of medicines refundable by National Health Insurance (B/1) and on the list of medicines approved for hospital use (B/1 and B/20) in the indications and at the dosages in the Marketing Authorisation.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (national procedure)	**Initial date: 27 February 2006**
Prescribing and dispensing conditions/ special status	**Not applicable**

ATC Classification	2012	
	B	Blood and blood-forming organs
	B05	Blood substitutes and infusion solutions
	B05B	Intravenous solutions
	B05BB	Solutions affecting the electrolyte balance
	B05BB02	Electrolytes with carbohydrates

02 BACKGROUND

The applicant is applying for inclusion of HYDRAPERF on the list of medicines refundable by National Health Insurance (B/1) and on the list of medicines approved for hospital use (B/1 and B/20). HYDRAPERF has had Marketing Authorisation in France for over 7 years under the name AGUETTANT 2.5% GLUCOSE 0.45% SODIUM CHLORIDE. This product has never been distributed.
In all its indications, this medicine may be administered intravenously. The "Posology" section in the Marketing Authorisation specifies that subcutaneous infusion may be used in the treatment of moderate cases of dehydration in the elderly. This is the only proprietary medicinal product whose Marketing Authorisation offers this possible route of administration.

03 THERAPEUTIC INDICATIONS

"- Rehydration in cases where water loss is higher than that of sodium chloride and other osmoles
- Prevention of intra- and extracellular dehydration
- Vehicle for therapeutic supplementation when compensating for abundant diuresis without carbohydrate overload."

04 DOSAGE

"Peripheral intravenous infusion or subcutaneous infusion, depending on weight, age, clinical condition, and water and glucose requirements.
The intravenous infusion dosage in adults is from 500 to 3000 ml/24 hours.

Subcutaneous infusion may be employed in the treatment of moderate dehydration in elderly subjects.
In general, it does not exceed 1500 ml/24 hours at one injection site, or 3000 ml/24 hours at two injection sites simultaneously.
A flow rate of 1 ml/min is recommended to reduce the risk of local oedema."

05 THERAPEUTIC NEED

Infusion solutions containing glucose and/or sodium chloride are used in particular for rehydration and for preventing dehydration. Many different proprietary medicinal products are available. These solutions are generally administered intravenously, especially in emergencies or in life-threatening situations (severe dehydration, ketoacidosis, antibiotic therapy, etc.).
Subcutaneous infusion (hypodermoclysis) is reserved for mild to moderate cases of dehydration or for preventing dehydration when the oral route cannot be used.[1] This is the only presentation with Marketing Authorisation for this route of administration.

06 CLINICALLY RELEVANT COMPARATORS

These are proprietary medicinal products containing 2.5% or 5% glucose or 0.9% sodium chloride, as well as solutions combining glucose and sodium chloride.
The actual benefit of these proprietary medicinal products is substantial. There is no difference between them in terms of improvement in actual benefit.

07 ANALYSIS OF AVAILABLE DATA

07.1 Efficacy

The prevention and treatment of rehydration is generally performed intravenously with the aid of solutions containing glucose and/or sodium chloride. Their efficacy is firmly established.
Hypodermoclysis using these solutions has also been around for several decades.
The applicant provided the results of a study in which the “convenience of the technique” administered by the subcutaneous route (SC) was compared with that administered by the intravenous route (IV) in the treatment of moderate dehydration in elderly subjects.

7.1.1 Slesak Study[2]

This open-label, single-centre randomised study in 2 parallel groups (2 routes of administration: SC and IV) evaluated the “convenience of the technique” as measured by carers and by patients. It was conducted in a geriatric department in Germany and included 96 patients with a mean age of 85 years.

The patients were randomised into 2 groups: 48 were treated subcutaneously and the other 48 intravenously. The infused solution was composed of 5% glucose serum and electrolytes at a semi-isotonic concentration (Iono-K®). The median duration of rehydration was 6 days, whichever technique was used. Every day, 1000 ml was infused intravenously and 750 ml subcutaneously.
The convenience of the technique was evaluated separately by carers and by patients on a scale of 1 (very bad) to 6 (very good). The publication did not provide any details or reasoning regarding the relevance of this scale.

[1] Les bonnes pratiques de soins en établissement d’hébergement pour personnes âgées dépendantes. Direction Générale de la Santé, Société Française de Gériatrie et Gérontologie. October 2007, 46-47.
[2] Slesak G et al, Comparison of subcutaneous and intravenous rehydration in geriatric patients: a randomised trial. J Am Geriat Soc 2003; 51:155–60.

No significant difference in “convenience” between the 2 techniques was observed by the patients. Carers judged the convenience of subcutaneous infusion to be greater. (The mean values for the groups treated by the SC or IV route are not available).
Thirteen of the group rehydrated subcutaneously were subsequently treated by venous infusion in order to be able to inject medicinal products (11 cases) or owing to insufficient resorption of the solution infused subcutaneously (2 cases).
In the group rehydrated intravenously, 17 patients had their IV infusion replaced by SC infusion owing to problems in maintaining venous access (8 cases), repeated displacement of the intravenous catheter (5 cases) or rejection by patients or carers (4 cases).

Conclusion
This study evaluated the convenience of the technique using the subcutaneous route in comparison to the intravenous route for the administration of glucose combined with sodium chloride in elderly patients. This did not rely on any clinical criteria.
There was no difference between the 2 techniques according to the patient-assessed convenience scale, but a difference was observed on the same scale by the carers. In view of the lack of any validation for the scale used, it is difficult to understand how meaningful this difference is.
There are accordingly no data on the effect of these rehydration methods on morbidity or mortality.

07.2 Adverse Effects

According to the current SPC, the following adverse effects may be observed: “hyperglycaemia, hypokalaemia, hypomagnesaemia, hypophosphataemia, hyperlactataemia and polyuria.

Some of the adverse effects may be associated with the technique of administration itself, including: fever, pain, local reaction or infection at the injection site, venous irritation, venous thrombosis or phlebitis extending from the injection site, extravasation and hypervolaemia.”

A warning states that “compatibility of the medicinal product with the subcutaneous route needs to be ascertained:

- if prolonged treatment is necessary, check for possible residual oedema after every infusion and, if one is found, change the administration site
- in heart failure patients, the infusion should be administered with caution and at a slow rate
- in the event of pain, always reduce the infusion rate, check that the needle is not in contact with muscle (in which case it cannot be mobilised) and check the quality of the injected fluid.”

07.3 Summary & discussion

No data have been provided on IV rehydration with HYDRAPERF; however, solutions of glucose or sodium chloride, or those combining both ingredients, have proved effective in the management of dehydration and in its prevention.
For many years, subcutaneous infusion (hypodermoclysis) has been used (off-label), particularly in elderly subjects, for the prevention or treatment of mild to moderate dehydration.
Data from a clinical study have shown only the convenience of the method as assessed by carers. It was not designed to show the subcutaneous route as having a clinical advantage (in terms of morbidity or mortality) over the intravenous route, especially in elderly subjects.
Adverse effects specific to the subcutaneous route of administration may be observed, such as pain at the injection site, oedema and haematoma.

08 THERAPEUTIC USE

Medicinal products containing glucose and/or sodium chloride have firmly established their efficacy in the treatment and prevention of dehydration.[3] They are administered intravenously or subcutaneously (not validated hitherto by any Marketing Authorisation except in the case of HYDRAPERF).
Rehydration by the parenteral route is an alternative to the oral route when the patient's cooperation cannot be relied upon. It is used in particular for the non-emergency rehydration of confused patients, so long as they are neither severely dehydrated nor in a state of shock.
Hypodermoclysis is used in particular in elderly subjects.[4] This subcutaneous route of administration is used in the prevention or treatment of dehydration when the oral route cannot be used and when venous access is difficult. HYDRAPERF is the only infusion solution whose Marketing Authorisation refers to the option of subcutaneous administration.

09 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above data and information, and following the debate and vote, the Committee's opinion is as follows:

[3] Les bonnes pratiques de soins en établissement d'hébergement pour personnes âgées dépendantes. Direction Générale de la Santé, Société Française de Gériatrie et Gérontologie. October 2007, 46-47.
[4] Assessment of medical devices for home infusion. Haute Autorité de Santé. September 2010.

09.1 Actual benefit

◗ Most often, the clinical situations associated with dehydration are complex and serious life-threatening disorders.
◗ These medicinal products are used as preventative or curative therapies.
◗ Their efficacy/adverse effects ratio in the Marketing Authorisation indications is high.

◗ There are many alternative medicinal products available when intravenous administration is an available option. HYDRAPERF is the only infusion solution whose Marketing Authorisation offers the option of subcutaneous administration in the treatment of moderate dehydration in elderly subjects.
◗ This medicinal product is a first-line therapy.

◗ Public health benefit:
Dehydration is the most commonly encountered metabolic disturbance in elderly subjects, whether they are home-based or institutionalised. It is estimated that 25% of institutionalised elderly febrile subjects present dehydration, often necessitating hospitalisation.[5] Physiological ageing makes elderly persons particularly sensitive to water and electrolyte variations (reduction in total water, hypodypsia, impaired renal function, etc.). Its prognosis is poor unless taken in hand at an early stage. Water and electrolyte imbalance can in fact be at the root of occasionally serious multivisceral complications (confusion, neurological disorders, falls, arterial vascular accidents, venous thrombosis, infections, etc.).

In France, the burden associated with dehydration may therefore be regarded as moderate. That of patients coming under the indication for HYDRAPERF, especially by the subcutaneous route, is slight owing to the fact that the indication is limited to the rehydration of elderly subjects suffering from mild to moderate dehydration and to the prevention of dehydration in at-risk patients.
The prevention and treatment of dehydration, in the elderly in particular, constitutes a public health need that falls within the framework of health measures designed to protect persons at risk and drawn up following the 2003 heatwave and its consequences for health (Heatwave Plan).
In light of the literature data available comparing the subcutaneous route – less invasive and therefore favoured when dealing with elderly subjects whose venous capital is often impaired – with the intravenous route, HYDRAPERF has not been shown to have any additional impact in terms of morbidity or mortality or quality of life. However, slightly or moderately dehydrated patients are likely to experience a benefit in terms of convenience.
Used in the context of the administration technique known as hypodermoclysis, HYDRAPERF could theoretically have a positive impact on the organisation of care. Its use outside the hospital setting (at home or in nursing homes) would sometimes help reduce the need for hospitalisation and its associated risks in elderly subjects (loss of independence, pressure sores, undernourishment, behavioural disorders, secondary infections, decline, etc.). However, this impact is nowadays very limited, given the established medical use of glucosaline solutions, which have been available for many years.

Consequently, in view of the available data, it is not expected that the proprietary medicinal product HYDRAPERF will benefit public health.

[5] Weinberg AD et al. Dehydratation and death during febrile episodes in the nursing home. J Am Geriatr Soc 1994; 42: 968-71.

Consequently, the Committee considers that the actual benefit of HYDRAPERF is substantial in the Marketing Authorisation indications.

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance (B/1) and on the list of medicines approved for hospital use (B/1 and B/20) in the indications and at the dosages in the Marketing Authorisation.

◗ Proposed reimbursement rate: 65%

09.2 Improvement in actual benefit (IAB)

HYDRAPERF does not provide any improvement in actual benefit (IAB V, non-existent) compared to other infusion solutions containing glucose and/or sodium chloride used in particular for rehydration and for preventing dehydration.

09.3 Target population

The target population of HYDRAPERF is that of patients requiring either prevention against or treatment for dehydration when the oral route cannot be used and when medication has therefore to be administered intravenously or subcutaneously.
To this population should be added patients needing a vehicle for giving medication by the intravenous route when compensating for abundant diuresis without carbohydrate overload.
There are no epidemiological data available to quantify these populations.

010 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging
Appropriate for the prescription conditions according to the indication, dosage and treatment duration.