HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

14 March 2007

SAVENE 20 mg/ml, powder for concentrate and diluent for solution for infusion
Box of 10 vials (CIP: 377 176-1)

Applicant : NOVEX PHARMA

dexrazoxane

List I
Orphan drug.
Medicinal product available only on restricted medical prescription. SAVENE must be administered under the supervision of a doctor competent in the use of anti-cancer chemotherapies.

Date of Marketing Authorisation: 14 August 2006 (centralised procedure)

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

Health Technology Assessment Division

1 CARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
dexrazoxane

1.2. Indication
SAVENE is indicated for the treatment of anthracycline extravasation

1.3. Dosage
Savene must be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents.

Savene should be given once daily for 3 consecutive days.

The recommended dose is:
Day one: 1000 mg/m2
Day two: 1000 mg/m2
Day three: 500 mg/m2

There is no experience with dose reduction/increase or modification of the schedule in the treatment of extravasation. For patients with a body surface area of more than 2 m2 the single dose should not exceed 2000 mg**.** The indicated dose should be administered as an intravenous infusion over 1-2 hours into a large vein in extremity/area other than the one affected by the extravasation. The first infusion should be initiated as soon as possible and within the first six hours after the accident. Cooling procedures such as ice packs should have been removed from the area at least 15 min before the Savene administration in order to allow sufficient blood flow. Treatment Day 2 and Day 3 should start at the same hour (+/- 3 hours) as on the first day.

Before infusion, Savene powder must be reconstituted with 25 ml sterile water to give a concentration of 20 mg dexrazoxane per ml sterile water. After reconstitution the solution should be further diluted in the bag with the Savene diluent.

Special populations:
Paediatric patients: Savene is not recommended for use in children due to a lack of data on safety and efficacy.

Patients with renal impairment: Savene has not been studied in patients with impaired renal function and its use in such patients is not recommended. Decreased renal function may lead to decreased rate of elimination and prolonged systemic exposure.

Patients with hepatic impairment: Savene has not been studied in patients with impaired hepatic function and its use in such patients is not recommended.

Elderly patients: Safety and efficacy have not been evaluated in the elderly.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

V: Various
V03: All other therapeutic products
V03A: All other therapeutic products
V03AF: Detoxifying agents for antineoplastic treatment
V03AF02: dexrazoxane

2.2. Medicines in the same therapeutic category

CARDIOXANE (dexrazoxane), indicated for the prevention of chronic cumulative cardiotoxicity caused by doxorubicin or epirubicin use in advanced and/or metastatic cancer patients after previous anthracycline containing treatment.

2.3. Medicines with a similar therapeutic aim

There are no medicinal products with a similar therapeutic aim.

3 ANALYSIS OF AVAILABLE DATA

The laboratory has submitted two studies:

- A phase II study (TT01),
- A phase III study (TT02).

Furthermore, the laboratory has cited 4 presentations of several cases (Langer 2000, Bos 2001, El-Saghir 2003 and El-Saghir 2004) that will not be used in this opinion.

3.1. Efficacy

o *Study TT01*

Objective: To assess the efficacy and safety of SAVENE in the prevention of surgery following extravasation (EV) of anthracyclines administered in a peripheral vein in 23 patients with malignant pathologies[1].

Methodology: Phase II, non-comparative study conducted on 23 patients treated for 3 days.

Inclusion criteria: Adult patients (average age 56 years), having previously received anthracycline treatment, with performance status (PS) 0-2, recent extravasation (<6 hours) confirmed by fluorescence microscopy of biopsy and requiring surgical intervention.

Treatment:
Treatment with SAVENE had to be started within 6 hours from the incident (1,000 mg/m^2) and be repeated after 24 hours (1,000 mg/m^2) and 48 hours (500 mg/m^2) as an IV infusion over one to two hours.

Primary endpoint: rate of surgical intervention.
According to the protocol SAVENE was regarded as effective if surgery could be avoided in 80% of cases. For 25 included patients, five (maximum) could undergo surgery (5/25 = 20%, 95% CI = 7-41).

[1] Breast cancer, lymphoma, gastric cancer, myeloma, Ewing sarcoma

RESULTS:
The study included 23 patients, 18 of which were evaluable; 5 patients were excluded from the analysis for the following reasons: four had negative biopsy results. One patient had an EV on a central venous catheter and could therefore not undergo a surgical biopsy procedure.

None of the 18 evaluable patients underwent surgical intervention following SAVENE administration.

o *Study TT02*

Objective: To assess the efficacy and safety of SAVENE to prevent progression of lesions and surgery following extravasation of anthracyclines administered in a peripheral vein in 57 patients with malignant pathologies[2].

Methodology: Phase III, non-comparative study, conducted on 57 patients treated over 3 days and monitored for 90 days.

Inclusion criteria: Adult patients (average age 55 years) treated with anthracyclines and presenting with performance status (PS) 0-2, recent extravasation (<6 hours) associated with pain, swelling and/or redness, confirmed by fluorescence microscopy of at least two biopsies.

Treatment:
Treatment with SAVENE had to be started within 6 hours from the incident (1,000 mg/m^2) and was repeated after 24 hours (1,000 mg/m^2) and 48 hours (500 mg/m^2) as an IV infusion over one to two hours.

Primary endpoints:
- Rate of surgical intervention,
- Rate of onset of tissue necrosis (verified by two investigators).

In this study the efficacy of SAVENE was compared to the rate of surgical intervention described in the literature. Historic data cited by the laboratory report the rate of recourse to surgery to be between 35% and 50% of patients with anthracycline EV (clinically suspected by not confirmed by biopsy). These incidence rates would be higher for patients with biopsy-confirmed EV. In study TT02, SAVENE was regarded as effective if surgery was necessary in less than 35% of patients treated with SAVENE.

Secondary endpoints: Onset of late sequelae, discontinuation of chemotherapy treatments.

RESULTS:
57 patients were included in the study and 36 patients were evaluable. Nine patients were excluded from the analysis in light of negative biopsy results and 12 due to deviation from the protocol (absence of biopsy results for 4 patients, no data available for the remaining eight patients).

[2] Breast cancer, lymphoma, myeloma and ovarian cancer.

Primary endpoints:
Only one of the 36 evaluable patients underwent a surgical intervention following administration of SAVENE. Necrosis was observed in this patient (2.8%).

Secondary endpoints:
Table 1: Rate of onset of late sequelae

Sequelae	**Number of patients N=36 (%)**
At least one sequela:	13 (36.1)
- Sensory disturbance	7 (19.4)
- Skin atrophy	4 (11.1)
- Pain	9 (25)
- Disfigurement	1 (2.8)
- Limitation of movement	3 (8.3)
Absence of sequelae	23 (63.9)

In the absence of a comparative arm, the results of these studies must be interpreted with caution.

3.2. Adverse events

The adverse events most frequently observed in the clinical studies were:
- Study TT01: Grade 1-2 injection-site reactions (61% of patients), grade 1-2 phlebitis (26% of patients),
- Study TT02: gastrointestinal disturbance (50.9% of patients), injection-site reaction (45.6% of patients), fatigue (12.3% of patients) and infection (28% of patients).

3.3. Conclusion

Efficacy and safety data for SAVENE are based on two non-comparative studies conducted on patients with malignant pathologies and extravasation of anthracyclines in a peripheral vein.
In study TT01 SAVENE prevented surgery in all 18 of the study's evaluable patients.
In study TT02 only one of the 36 evaluable patients underwent surgical intervention following administration of SAVENE.

The main adverse events observed in the two studies were injection-site reactions and gastrointestinal disturbances.

The Transparency Committee emphasized the methodological limitations of these studies:
- Lack of information for 12/57 patients excluded from the analysis (21%) in study TT02,
- Absence of a comparative arm that does not allow for the actual rate of surgical interventions prevented by SAVENE to be known.

Finally, the studies presented relate to the usefulness of the medicinal product during anthracycline extravasations in a peripheral vein. However, at the present time, chemotherapy treatments are primarily administered via a central venous access (implantable chamber, central venous catheter); therefore the benefit of this medicinal product in current practice is difficult to assess.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Skin necrosis following extravasation of anthracyclines is a rare complication that can be serious and debilitating.

This medicinal product is intended as curative treatment.

The efficacy/undesirable effect ratio of this medicinal product is substantial.

SAVENE is a first-line therapy.

There are no treatment alternatives.

Public Health Benefit:

In terms of public health, the burden caused by anthracycline extravasation, (complications that are sometimes very serious) is low due to restricted number of affected patients.

Improving the management of cancer chemotherapy complications is a necessity falling within the scope of an identified need (GTNDO* priority).

In light of the clinical trial results it is expected that SAVENE will have an impact in terms of morbidity (particularly on the frequency of surgical interventions). However, it is difficult to quantify this impact in light of the uncertainty regarding the product's benefit in common practice to the extent that trials involved only patients undergoing peripheral access chemotherapy treatments. However, chemotherapies are currently nearly all administered by central venous access. Extrapolation of the trial results to the actual situation is therefore not guaranteed.

SAVENE is expected to provide a partial response to the identified requirement.

As a result, this medicinal product is expected to have a public health benefit. This benefit is low.

* Groupe Technique National de Défintion des Objectifs (DGS- 2003)

The actual benefit provided by SAVENE in the treatment of anthracycline extravasation is substantial.

4.2. Improvement in actual benefit

In light of the absence of treatment alternatives and despite the methodological inadequacies of the studies contained in the file, the Transparency Committee considers that SAVENE provides a moderate improvement in actual benefit (IAB III) in the treatment of anthracycline extravasations.

4.3. Therapeutic use[3,4,5]

Skin necrosis following extravascular chemotherapy injection, particularly of cytotoxic drugs (anthracyclines), is a rare complication that can be serious and debilitating.

[3] « Evaluation de la qualité de l'utilisation et de la surveillance des chambres à cathéter implantables », Recommandations ANAES 2000, Service « Evaluation des pratiques professionnelles ».
[4] CCLIN « Recommandations pour la manipulation des médicaments cytotoxiques » Juillet 2002
[5] EPAR SAVENE – EMEA 2006

The clinical picture of anthracycline extravasation generally evolves in several phases:
- The initial phase is characterised by immediate pain,
- Oedema and swelling,
- Erythema,
- Blistering followed by a marked brownish induration lasting for days to months.

In some patients, if treatment is not immediately administered, severe complications may ensue: ulceration of the induration after 1-4 weeks occurs, with a tendency to extend to deep structures and underlying tendons and joints.

The ulcer is largely avascular. The risk of ulceration is strongly related to the concentration and amount of extravasated product. Long-term complications include pain, contractures, dystrophy and loss of function of the affected limb.

Current treatment of anthracycline extravasation is based on non-surgical methods, in accordance with the recommendations of the *Comité National Hospitalier d'Information sur le Médicament* (CNHIM)[6] [French national drug information centre]. It recommends, in particular, the immediate discontinuation of the infusion and aspiration of the residual cytotoxic product at the infusion site before removing the catheter.

A few recent studies have brought to light the benefit of an emergency surgical treatment, consisting of aspiration-lavage in case of iatrogenic extravasation with cytotoxic or hyporosmolar solutions. The aspiration technique combined with abundant irrigation (500 ml to 2 L of physiological saline solution), undertaken within 6 to 8 hours, results in almost complete recovery in the absence of iatrogenic sequelae.

In most institutions, local cooling is undertaken to cause vasoconstriction, and hence prevent the product from spreading and provide pain relief. The administration of corticosteroids and dimethylsulfoxide (DMSO, a solvent that enhances skin permeability) is also undertaken to increase skin permeability and thus facilitate recovery of the product.

SAVENE may prevent surgical intervention in limited forms, upon condition that it is administered within 6 hours following the incident.

4.4. Target population

The target population is composed of cancer patients with anthracycline extravasation.
Considering the primary indications for treatment with anthracyclines[7] (daunorubicin, doxorubicin, epirubicin, idarubicin, pirarubicin), the maximum population exposed to this type of product may be estimated from the number of patients with:
- Breast cancer: 42,000 patients,
- Hodgkin's and non-Hodgkin's lymphoma: 11,267 patients,
- Lung cancer: 27,743 patients,
- Acute and chronic leukaemias: 6,243 patients,
- Bladder, ovarian, stomach, oesophageal, pancreatic and liver cancers: 38,216 patients,
- Otorhinolaryngological cancers: 19,611,

i.e., a maximum total population of approximately 145,000 patients.

According to the EMEA, published data estimates the incidence of anthracycline extravasation to be between 0.1 and 1% of treated patients.

Thus the maximum target population of SAVENE would be comprise between 145 and 1,450 patients per year.

[6] Comité National Hospitalier d'Information sur le Médicament "Cytotoxiques: utilisation pratique" Revue Eval Med 1998 ; 19 :2-3.
[7] DGS/GTNDO 2003

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the indication and at the dosage in the Marketing Authorisation.

The Transparency Committee requests that a study on the treatment of extravasations in cancer patients treated with anthracyclines be undertaken.

The objective of such a study would be to describe, under real clinical conditions:

- Patient characteristics (gender, age, type of cancer, etc.),
- Method and area of anthracycline administration (peripheral or central access),
- Characteristics of the extravasation and its potential complications,
- Therapeutic management of the extravasation,
- Impact of treatments undertaken (including or excluding SAVENE) on extravasation sequelae, and in particular on the rate of surgical interventions necessary.

The duration of the study, determined by an independent scientific committee, must be justified and sufficient to meet the requirements stipulated by the Committee.