HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

12 September 2007

INFRACYANINE 25 mg/10 ml, powder and solvent for solution for injection
25 mg vial with one 10 ml ampoule of solvent (CIP: 360 841-7)

Applicant: SERB

Indocyanine green monopic

ATC: V08B
List I

Marketing Authorisation (MA) date:
- April 16, 2003
- Amendments:
  - November 7, 2005 (MA wording changed)
  - November 14, 2005 (dosage and method of administration)

Approved for use by hospitals and various public services

Reason for request:
- Examination of the change in the wording of the indications in the Marketing Authorisation, specifying “study of choroidal vessels using infrared ocular angiography” as an indication.
- Inclusion on the list of medicines reimbursed by National Insurance

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Indocyanine green monopic.

1.2. Indications

- Study of choroidal vessels using infrared ocular angiography, particularly for age-related macular degeneration (ARMD), degenerative myopia and other causes of choroidal neovascularisation: central idiopathic chorioretinopathy, macular oedema, inflammatory diseases of the choroid, familial and hereditary degenerative diseases, and choroidal tumours.
- Determination of liver blood flow and functional hepatic reserve by carrying out clearance tests.
- Measurement of the circulating blood volume and cardiac output; non-invasive determination is particularly recommended for newborn babies, infants and ICU patients.

1.3. Dosage

Direct intravenous use.
The total injected dose must not exceed 0.5 mg/kg for adults.

Where it is not disposable (glass), the equipment used to inject the medication must be perfectly sterile and must be rinsed with the solution used to dissolve the lyophilisate.

Study of choroidal vessels using infrared ocular angiography:
The dose administered to each patient depends on the characteristics of the equipment used: excitation light, filters, detection system. This dose is calculated at a rate of 0.25 to 0.5 mg/kg based on the patient's weight: the average is 0.35 mg/kg.

The doses are generally as follows:
- Digital angiography with infrared camera detection: 25 mg (10 ml) of indocyanine green for a patient weighing 70 kg.
- Scanning laser ophthalmoscope: 12.5 mg (5 ml) of INFRACYANINE for a patient weighing 70 kg

4 ml of this solution is injected as a bolus injection (in 5 seconds) for the early phase of the angiography (0 – 6 minutes). Slowly inject the rest of the syringe in the 6th minute. A very small volume of solution (0.1 ml or less) can be injected in the late phase (in the 20th minute) in order to detect lesions relating to vascular structures.

Other indications: See SmPC

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2007)

V : Various
V08 : Contrast agents
V08B : Iodine-free contrast agents

2.2. Medicines in the same therapeutic category

There are no comparable medicinal products in the same pharmacotherapeutic class with the same indications.

2.3. Medicines with a similar therapeutic objective

FLUORESCEIN SODIUM FAURE 10%, solution for injection, indicated in fluorescein angiography of the ocular fundus.

Other diagnostic method with the same therapeutic objective: Optical coherence tomography (OCT).

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The change in the MA description is based on literature data.
The company submitted 7 published clinical studies, 4 of which involved patients suffering from ARMD (Guyer DR, 1994; Lim JI, 1995; Slakter JS, 1994 and Brancato R, 2000), 1 involved patients suffering from severe myopia and 2 involved patients with choroidal tumours (haemangiomas, Schalenbourg, 1996 and 2000).
In the studies by Slakter JS (1994) and Brancato R (2000), indocyanine green (ICG) angiography was used for guiding treatment using laser photocoagulation.

ARMD

Guyer DR study (1994):

This non-randomised, prospective study compared indocyanine green angiography with fluorescein angiography in terms of the percentage of patients with occult choroidal neovascularisation (CNV) and the patients eligible for treatment using laser photocoagulation. Both types of angiography were performed consecutively on the same group of patients suffering from ARMD in the 50+ age category (n=503).

Comment: This study cannot be taken into account without a hypothesis for the statistical analysis stipulated in the protocol and in view of the fact that the risk of having false positives was not examined. No conclusions can be drawn from this study in order to evaluate the benefits of indocyanine green angiography over fluorescein angiography.

Lim JI study (1995):

This non-randomised, retrospective study compared the decisions to treat 77 eyes affected by ARMD with occult CNV with laser photocoagulation or surgery following review of the fluorescein and indocyanine green angiograms.

Comment: This retrospective study involving a small number of patients and without statistical hypotheses cannot be taken into account.

Slakter JS study (1994):

This non-comparative, prospective study evaluated the clinical benefits of laser photocoagulation guided by indocyanine green angiography on 347 patients with clinical and fluorescein angiography-based signs of occult CNV secondary to ARMD.

Comment: This non-comparative study does not reveal the benefits of indocyanine green angiography for guiding treatment using laser photocoagulation.

Brancato R study (2000):

This non-comparative, prospective study evaluated the clinical benefits of laser photocoagulation guided by indocyanine green angiography on eyes for which fluorescein angiography had revealed occult CNV in 79 patients suffering from ARMD with or without pigment epithelium detachment.

Comment: This non-comparative study does not reveal the benefits of indocyanine green angiography for guiding laser photocoagulation treatment.

Pathological myopia

Axer-Siegel R study (2004):

The objective of this retrospective study was to compare the images obtained using indocyanine green angiography and fluorescein angiography in cases of pathological myopia in 35 eyes by detecting signs of peripapillary atrophy, chorioretinal atrophy, retinal haemorrhage, rupture lines and choroidal neovascularisation.

Comment: This retrospective study involving a small number of patients and without a statistical analysis cannot be taken into account.

Choroidal tumours (haemangiomas)

Schalenbourg A study(1996):

The objective of this study of 50 patients was to determine whether a characteristic indocyanine green angiogram exists in cases of non-pigmented choroidal tumours.

Comment: This descriptive study does not show the diagnostic efficacy of indocyanine green angiography.

Schalenbourg A study (2000):

The objective of this study of 75 patients was to determine whether a characteristic indocyanine green angiogram exists in cases of choroidal haemangiomas and variant forms.

Comment: This descriptive study does not show the diagnostic efficacy of indocyanine green angiography.

3.2. Adverse events

Indocyanine green was tolerated well in all the studies provided.

The SPC mentions that most of the reported adverse events are temporary:

- Uncommon events: nausea or vomiting
- Rare events: feeling of weakness, hot flushes, excessive sweating, skin reactions (skin rash, urticaria or isolated pruritis)
- Exceptional cases: Quincke's oedema, anaphylactic shock following concomitant administration of indocyanine green and fluorescein.

Temporary colouration of the integuments was observed in the case of accidental paravenous injection.

3.3. Conclusion

The studies provided relating to ARMD, pathological myopia and haemangiomas of the choroid can only be regarded as exploratory due to their weak methodological quality.

The diagnostic efficacy of indocyanine green was not evaluated according to the criteria required for diagnostic evaluation.

Indocyanine green was tolerated well in the studies. The adverse events mentioned in the SPC are uncommon or rare, and are temporary. In exceptional cases, Quincke's oedema or anaphylactic shock was observed following concomitant administration with fluorescein.

No clinical data was provided in the other indications: central idiopathic chorioretinopathy, macular oedema, inflammatory diseases of the choroid and familial and hereditary degenerative diseases.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Indocyanine green angiography is used on patients suffering from diseases of the retina, particularly age-related macular degeneration (ARMD) and degenerative myopia.

ARMD is a chronic degenerative disease occurring in patients in the 50+ age group. The forms known as "exudative" or "wet" result in the formation of areas of choroidal neovascularisation leading to the progressive loss of central vision.

Degenerative myopia is a complication of severe or pathological myopia that is characterised by a refractive error of more than 6 dioptres and an axial ocular globe length of more than 26 mm; associated with degenerative and progressive chorioretinal lesions throughout the patient's life. It is one of the main causes of severe impairment of central visual acuity, which can reach -30 dioptres or more, and is the main cause of neovascularisation in patients under 50 years of age.

The other diseases involved are: central serous idiopathic chorioretinopathy, macular oedema, inflammatory diseases of the choroid, familial and hereditary degenerative diseases and choroidal tumours.

These diseases are disabling and bring about a marked deterioration in quality of life.

Indocyanine green in the form of a solution for injection is a medicinal product used for diagnostic purposes.

Public health benefit:

Age-related eyesight disorders (other than cataracts and glaucoma) represent a considerable public health burden. ARMD, pathological myopia and the other causes of CNV represent a moderate public health burden in that these diseases only affect some of the patients suffering from age-related eyesight disorders.

Improving the diagnostic certainty of ocular angiography in these diseases is a diagnostic requirement that may have important implications in terms of public health.

However, a review of the available data shows that this product is not expected to have an impact in terms of improving the diagnostic efficacy of ocular angiography or in terms of morbidity.
Furthermore, due to uncertainty about the level of agreement among ophthalmologists with regard to the reading of angiograms, there is no guarantee that the results of the studies can be transposed into actual practice.

We cannot assume, therefore, that this technique meets the identified public health need.

Consequently, in view of the data that are available, this product is not expected to benefit public health.

Given the lack of data for the evaluation of the diagnostic efficacy of indocyanine green angiography, the efficacy/undesirable effects ratio cannot be evaluated.

Indocyanine green angiography is a second-line diagnostic procedure used to confirm the presence of occult CNV that was suspected during a clinical examination and an initial fluorescein angiography. ICG angiography is also used to verify the absence of persistent or recurrent occult CNV following laser photocoagulation treatment.

There is no alternative medication.

The actual benefit is substantial.

4.2. Improvement in actual benefit

INFRACYANINE 25 mg/10 ml, powder and solvent for solution for injection does not provide any improvement in actual benefit (IAB V) in the study of choroidal neovessels using infrared ocular angiography, pending the results of the study currently in progress.

4.3. Therapeutic use

Indocyanine green angiography is primarily used in the diagnosis of ARMD. It can be diagnosed by fluorescent angiography, which shows up the choroidal neovessels (CNV) that are present in the exudative form of ARMD. ICG angiography is a supplementary technique for showing the presence of suspected occult CNV and for recording its exact topography.
ICG angiography is also used to obtain follow-up data on patients who have been treated in order to determine CNV persistence (presence in the treated area less than 6 months post-treatment) or recurrence (appearing 6 months or more after laser treatment).

4.4. Target population

The change in the wording of the indication does not change the previously estimated target population (Opinion of April 13, 2005), represented for the most part by patients suffering from exudative ARMD, for whom the presence of choroidal neovascularisation must be confirmed and specific contour details recorded.

4.5. Transparency Committee recommendations

The Transparency Committee recommends maintaining on the list of medicines approved for use by hospitals and various public services in the indication for the study of choroidal vessels using infrared ocular angiography, as amended by the Marketing Authorisation revision dated November 7, 2005.

The Transparency Committee recommends inclusion on the list of pharmaceutical products reimbursed by National Insurance.

Packaging: Appropriate for the prescribing conditions.

Reimbursement rate: 65%