HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

23 April 2014

CARMYNE 40 mg/5 ml, solution for injection

B/10 vials (glass) of 5 ml (CIP: 34009 275 167 3 3)

Applicant: SERB

INN	indigotin (indigo carmine)
ATC Code (2012)	V04CH02 (Tests for renal function and ureteral injuries)
Reason for the request	**Inclusion**
List concerned	**Hospital use** (French Public Health Code L.5123 2)
Indication concerned	**"This medicinal product is for diagnostic use only. CARMYNE is indicated in the intraoperative detection of ureteral** injuries during abdominal and pelvic **surgery. "**

Actual Benefit	**The actual benefit of CARMYNE is substantial.**
Improvement in Actual Benefit	**The Committee considers that CARMYNE provides a moderate improvement in actual benefit (level III) in the intraoperative detection of ureteral** injuries during abdominal and pelvic **surgery.**
Therapeutic use	**Surgeons should only use indigotin if there is a suspicion of intraoperative ureteral injury or when a ureteral wound is likely during radical surgical procedures (prostatectomy, for example) and if a fistula is suspected. In such cases, indigo carmine is considered as a first-line treatment.**
Target population	**The target population of CARMYNE can be estimated at 127,000 patients/year.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	12/08/2013 (national procedure)
Prescribing and dispensing conditions/special status	List I Diagnostic medicinal product Medicinal product reserved for hospital use

ATC Classification	2012	
	V	Various
	V04	Diagnostic agents
	V04C	Other diagnostic agents
	V04CH	Tests for renal function and ureteral injuries
	V04CH02	indigo carmine

02 BACKGROUND

Review of the application for inclusion of the proprietary medicinal product CARMYNE 40mg/5ml, solution for injection, on the list of medicines approved for hospital use.

Indigotin (indigo carmine), active ingredient of CARMYNE, is a diagnostic medicinal product used clinically for a number of years in the intraoperative detection of ureteral injuries during abdominal and pelvic surgery. When indigotin (indigo carmine) is intravenously administered, induces dark blue colored urines within 5 to 15 minutes after injection. This intense coloration enables to display the urinary tract and detect any lesions of the urinary tract.

For twenty years, indigotin (indigo carmine) has been marketed under the name indigo carmine 0.8%.
To obtain regulatory status for this medicinal product, SERB has developed a Marketing Authorisation (MA) application dossier in collaboration with ANSM [National Medicines and Health Products Safety Agency]. A MA was granted on 12 August 2013.

03 THERAPEUTIC INDICATIONS

"This medicinal product is for diagnostic use only. CARMYNE is indicated in the intraoperative detection of ureteral injuries during abdominal and pelvicsurgery. "

04 DOSAGE

"This product is to be injected by slow intravenous route whilst monitoring arterial pressure and heart rate. The recommended initial dose is one ampoule of 5 ml by slow intravenous injection.
A second ampoule may be injected 20 to 30 minutes after the first injection if necessary.

In children
The dose is half an ampoule per injection.

In patients with renal impairment

In patients with a clearance of creatinine ≥ 10 ml/min, indigotin (indigo carmine) may be administered.
In patients with a clearance of creatinine < 10 ml/min, the time until indigotin (indigo carmine) appears in urine may be delayed by several minutes. The administration of Indigotin should therefore not be renewed.

In the elderly
No dosage adjustment is necessary.

In patients with liver impairment
The excretion of CARMYNE is mainly renal. Although there is no data in patients with hliver impairment, no dosage adjustment is necessary.

Method of administration
Filtration is recommended with a filter of maximum 0.45 µm. ".

05 THERAPEUTIC NEED

During abdominopelvic surgery, damage to the urinary tract and, specifically, ureteral injuries may occur.

For twenty years, use of dyes including indigotin (marketed under the name indigo carmine 0.8%) allowed the detection of intraoperative ureteral injuries. However, such use was off-label as none of them were approved in France.
CARMYNE is the first to obtain a Marketing Authorisation in this indication.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

There are no clinically relevant comparators for indigotin with a Marketing Authorisation in this indication. However, some other dyes are used off-label: patent blue and methylene blue.

06.2 Other health technologies

The medical device (MD) Blue Marker Aguettant 10 mg/ml is a methylene blue-based dye. The indications claimed for this MD are delineation of tissues and surgical specimens as well as the leak test for urinary sutures. It cannot be administered intravenously and does not have an indication in the detection of ureteral injuries.

◗ Conclusion
There are no clinically relevant comparators with Marketing Authorisation in this indication.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Not applicable

08 ANALYSIS OF AVAILABLE DATA

08.1 Efficacy

Evaluation of the intraoperative diagnostic accuracy of indigo carmine (CARMYNE) is based on a meta-analysis conducted by the company and which included articles published until January 2010.

8.1.1 Study design

The objective of this meta-analysis[1] was to estimate the diagnostic performance of the intravenous administration of indigotin in combination with endoscopic technics to detect potential ureteral injuries occurring during gynaecological interventions .
The chosen evaluation criteria were: sensitivity, specificity, positive (LR+) and negative (LR-) likelihood ratios, and positive (PPV) and negative (NPP) predictive values of the diagnostic test, as recommended by the EMA.[2]

The selection criteria for the studies were as follows:
- inclusion of women undergoing gynaecological surgery without any restriction on the type of surgery or surgical approach (vaginal, abdominal, laparoscopic).
- systemic use of intravenous indigotin (whatever the dose) in combination with endoscopic procedures.
- post-operative follow-up in the study design: there is no gold standard diagnostic test for the detection of ureteral injuries during gynaecological surgical procedures, yet comparison with a gold standard test is the basis for evaluating the diagnostic validity of a test.[1] This comparison is used to determine the test's ability to correctly classify subjects (number of true and false positives and number of true and false negatives). In its absence, post-operative patient follow-up is used to detect any ureteral complication.
- studies with a number of prospective or retrospective false positives and false negatives, and case-control studies.
- The "case studies" were excluded.

Evaluation of the methodological quality of the studies was performed with the checklist QUADAS (Quality Assessment of Diagnostic Accuracy Studies). This is a gold standard methodological assessment tool for diagnostic accuracy studies available when the meta-analysis was conducted (2010).

8.1.2 Results

Overall, 15 studies were included in the meta-analysis (n=5830 patients).

The sensitivity and specificity of each study were grouped. The results obtained were as follows:
- **overall sensitivity** (ability of the test to correctly diagnose patients with an injury) = 0.96, 95% CI = [0.91; 0.99]. No heterogeneity was detected.
- **overall specificity** (ability of the test to correctly diagnose patients without an injury) = 0.99, 95% CI = [0.99; 1.00]. Statistical heterogeneity was detected and taken into account by the authors, but this did not have any clinically significant impact. However, it should be noted that the authors did

[1] SERB - CARMYNE 40 mg/5 ml, injectable solution. Clinical Report MA-IC-01.
[2] EMEA: Guideline on clinical evaluation of diagnostic agents. CPMP/EWP/1119/98/Rev.1. 23 july 2009. Available online: [URL]: http://qibawiki.rsna.org/images/1/1a/EU.2009.08.04_Guideline_on_Clinical_evaluation_of_diagnostic_agents.pdf

not define the trial or seek the factor (population, methodological quality, etc.) causing this heterogeneity, and consequently did not perform a subgroup analysis.

An ROC (Receiver Operating Characteristics) curve was created. It represents the calculation of all sensitivity-specificity pairs in the studies included in this meta-analysis. The point cloud obtained was condensed on the upper left part of the graph corresponding to a high level of diagnostic performance of the test.

The likelihood ratios are parameters quantifying the contribution of the test when it is used clinically. They represent the ratio between the probability of a given outcome for the test in subjects with ureteral injury and in subjects without.
- positive (R+) likelihood ratio = 214, 95% CI = [75.6; 606.4] which means that the subjects with ureteral injury are 214 times more likely to have a positive test than the subjects without.
- negative (R-) likelihood ratio = 0.134, 95% CI = [0.078; 0.230] which means that the subjects with ureteral injury are almost 10 times less likely to have a negative test than the subjects without.
A diagnostic test is considered useful for confirming the presence of a complication or disease if its LR+ is > 10 and for confirming the absence of a complication or disease if its LR- is < 0.1.

Finally, the PPV (probability that the complication/disease is present if positive test) and NPV (probability that the complication/disease is absent if negative test) were estimated from the sensitivity and specificity. They do not represent the intrinsic values of the test because they primarily depend on the prevalence of the complication/disease sought in the patient sample. However, they are very useful for evaluating the use of the test in clinical practice.
In this case, this prevalence varies depending on the type of surgical procedure. For a prevalence varying from 0.05% to 7.50%, the PPV was between 10.7% and 95.1% and the NPV was between 100 and 99%.

It is interesting to observe that the series only cover the indication for gynaecological surgery and that other indications exist, particularly for digestive surgery and urology without necessarily using cystoscopy. Indeed, blue highlighting through a ureteral fistula during a laparotomy or coelioscopy is a common screening method for a ureteral wound.

08.2 Safety

8.2.1 Summary of product characteristics

"The most common adverse effects of indigotin (indigo carmine) are mainly related to its alpha-adrenergic properties and are of a cardiovascular origin. Other idiosyncratic effects, such as changes in blood pressure or heart rate or anaphylactoid effects, have also been described. Serious adverse effects of indigotin (indigo carmine) are very rare.

Cardiac disorders
Very frequent:
- transient hypertension
- bradycardia

Very rare:
- tachycardia
- hypotension
- atrioventricular block

Respiratory, thoracic and mediastinal disorders
Very rare:
- dyspnoea
- bronchial hyperreactivity

Skin and subcutaneous tissue disorders
Very rare:
- skin rash and erythema
- skin discolouration

Immune system disorders
Very rare:
- anaphylactoid reactions

No case of overdose has been reported in the literature for doses up to 80 mg indigotin (indigo carmine) administered intravenously.
Any overdose could induce an hypertensive crisis and severe bradycardia. In case of overdose, peripheral vasodilator therapy may be considered. "

The company has also provided a number of articles mentioning the reported cases. These data from the literature cannot be taken into account for an accurate assessment of the safety of this proprietary medicinal product.

08.3 Summary & discussion

Assessment of the diagnostic performance of indigo carmine (CARMYNE) in the intraoperative detection of ureteral injuries during abdominal and pelvicsurgery is based on a meta-analysis conducted by the company and which included articles published until January 2010. Overall, 15 studies were included in the meta-analysis (n=5830 patients).

The results obtained were as follows:
- overall sensitivity = 0.96, 95% CI = [0.91; 0.99]
- overall specificity = 0.99, 95% CI = [0.99; 1.00]
- positive likelihood ratio (LR+) = 214, 95% CI = [75.6; 606.4]
- negative likelihood ratio (LR-) = 0.134, 95% CI = [0.078; 0.230]
- for a prevalence of intraoperative ureteral injuries varying from 0.05% to 7.50%, the positive predictive value (PPV) varied from 10.7% to 95.1% and the negative predictive value (NPV) varied between 100 and 99%.

This test presents very good diagnostic performance.
Assessment of the diagnostic test is done on its parameters of diagnostic validity, but also through its impact on the prognosis and management of patients (see "Public health benefit" part, "Actual benefit" section).

Assessment of the safety of indigotin is based on information provided in the SPC.
The most common adverse effects of indigotin are cardiovascular (arterial hypertension, bradycardia, hypotension, tachycardia, atrioventricular block) and are linked to its pharmacological properties. This causes an increase in total peripheral resistance through direct stimulation of the alpha-adrenergic receptors or release of catecholamines.
Very rare anaphylactoid reactions were described. Some of them were serious, even fatal. These reactions may occur in patients with unremarkable history.

09 THERAPEUTIC USE

Abdominopelvic surgery is varied. The main surgical procedures responsible for ureteral injuries and likely to require the use of indigotin (indigo carmine) are hysterectomies, surgery for pelvic organ prolapse, surgery for urinary incontinence, difficult radical prostatectomies with large median lobe exposing injuries in ureteral orifices, difficult resections of abdominal tumours associated with a risk of wound, but also large bladder tumours engulfing trigone surgery or even colic surgery with no visualisation of the ureter.

The first consequence of a post-surgical ureteral complication involves reoperations. In terms of clinical consequences, the undetected iatrogenic ureteral injuries present various degrees of morbidity: psoas abscess, urinary tract infection, ureteral necrosis, urinary peritonitis, uretero-vaginal fistula or loss of renal function.

Currently, there is no national or international recommendation on the role of indigotin (indigo carmine) and its use during gynaecological and urological surgery.

According to experts, surgeons should only use indigotin if there is a suspicion of intraoperative ureteral injury or when a ureteral wound is likely during radical surgical procedures (prostatectomy, for example) and if there is a fistula. In such cases, indigotin (indigo carmine) is considered as a first-line treatment.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

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

010.1 Actual Benefit

◗ The consequences of undetected iatrogenic ureteral injuries are varied and present various degrees of morbidity: psoas abscess, urinary tract infection, ureteral necrosis, urinary peritonitis, uretero-vaginal fistula or loss of renal function.
◗ This medicinal product is intended for diagnostic use.
◗ The benefit/risk balance is high.
◗ There are no diagnostic alternatives.
◗ It is a first-line treatment in case of suspection of ureteral injury during abdominal and pelvic surgery.

◗ Public health benefit: The burden represented by ureteral injuries of abdominal and pelvic surgery is difficult to quantify because of the absence of reliable epidemiological data. It can be considered at best as moderate (CARMYNE would only be used during abdominopelvic surgical procedures most at risk of ureteral complications).
The reduction of the complications linked to surgery is listed in the national patient safety program 2013-2017 and represents a public health need.
Given the available data, a positive impact is expected for CARMYNE in terms of patient morbidity for this type of surgery due to an increased perioperative rate of detection of ureteral injuries leading to immediate treatment during the surgical procedure of patients presenting this type of complication. This impact is difficult to quantify due to the long-standing use of this method.
The expected impact on patients' quality of life has not been documented.
The impact which might be expected in terms of the organisation of care (with a lower hospitalisation rate and reintervention rate in patients with ureteral injury and who have been treated early) has not been documented.
The extrapolation of data to current practice is not totally guaranteed because of the long-term existence of the data presented.
CARMYNE therefore provides a partial response to the identified public health need.

Overall, CARMYNE could have an impact on public health. However, in the absence of recent data, that impact cannot be quantified.

Taking account of these points, the Committee considers that the actual benefit of CARMYNE is substantial in the intraoperative detection of ureteral injuries during abdominal and pelvic surgery.

The Transparency Committee recommends inclusion on the list of medicines approved for hospital use in the indication and at the dosages of the Marketing Authorisation.

010.2 Improvement in actual benefit (IAB)

The Committee considers that CARMYNE provides a moderate improvement in actual benefit (level III) in the intraoperative detection of ureteral injuries during abdominal and pelvic surgery. Surgeons must only use it if there is a suspicion of intraoperative ureteral injury or when a ureteral wound is likely.

010.3 Target population

The company submitted the annual sales data for this proprietary medicinal product in France in 2013. Moreover, the company conducted a study in 2006 (PMS-IC-02), the objective of which was to collect data on the mean dose used during surgical procedures. The dose that is mainly used is one ampoule, i.e. 40 mg, and in 8% of cases, two ampoules, i.e. 80 mg, are used or even, in 7% of cases, half an ampoule is used (dosage in children).
Thus, the number of surgical procedures requiring the use of CARMYNE may be estimated at 127,000/year.

From these data, the target population for CARMYNE could be estimated at 127,000 patients/year.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging

Appropriate for the prescribing conditions as regards the indication, dosage and treatment duration.