HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

17 April 2013

CLOROTEKAL10 mg/ml, solution for injection

B/10 vials of 5 ml (CIP: 34009 222 958 6 2)

Applicant: NORDIC PHARMA

INN	chloroprocaine
ATC code (2012)	N01BA04 (local anaesthetics)
Reason for request	**Inclusion**
List concerned	**Hospital Use** (French Public Health Code L.5123-2)
Indications concerned:	**"Intrathecal anaesthesia in adults before planned surgery not lasting in excess of 40 minutes."**

Actual Benefit	**The actual benefit of CLOROTEKAL in the Marketing Authorisation indication is substantial.**
Improvement in Actual Benefit	**CLOROTEKAL does not provide an improvement in actual benefit (non existent IAB) compared with other intrathecal local anaesthetics.**
Therapeutic use	**CLOROTEKAL is an alternative to other local anaesthetics in adults undergoing planned surgery not lasting in excess of 40 minutes who are to be given intrathecal anaesthesia.**
Recommendations	**The Committee approves inclusion on the list of proprietary medicinal products approved for hospital use in the indication and at the doses in the Marketing Authorisation.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Initial date (decentralised procedure): 12 November 2012
Prescribing and dispensing conditions/special status	Medicinal product reserved for hospital use

ATC Classification	2012	
	N	Nervous system
	N01	Anaesthetics
	N01B	Local anaesthetics
	N01BA	Aminobenzoic acid esters
	N01BA04	chloroprocaine

02 BACKGROUND

The company is requesting that CLOROTEKAL be included on the list of medicinal products approved for hospital use. CLOROTEKAL was granted a European MA on 12 November 2012.
This medicinal product is positioned as an alternative to other local anaesthetics administered intrathecally: ropivacaine, bupivacaine and levobupivacaine.

03 THERAPEUTIC INDICATION

“Intrathecal anaesthesia in adults before planned surgery not lasting in excess of 40 minutes.”

04 DOSAGE

The posology should be established individually depending on specific patient features. In determining the dose, the patient's physical state and concomitant administration of other medicinal products should be taken into account.
The duration of action is dose-dependent.
The doses below are recommended for adult patients of average height and weight (approximately 70 kg) to obtain effective block from a single dose. Large inter-individual variations are seen in intensity and duration of action. The anaesthetist's experience and knowledge of the patient's general health are essential factors in determining the dose.
The following dosage recommendations are given:

Dosage in adults:

	ml	mg	Average duration of action (minutes)
Sensory block level required: T10	4	40	80
	5	50	100

The maximum recommended dose is 50 mg (=5 ml) of chloroprocaine hydrochloride.

Special populations
A reduction in dose is recommended in patients in poor general health.
The posology should also be reduced in the presence of concomitant diseases (such as vascular obstruction, arteriosclerosis, diabetic polyneuropathy).

Paediatric population
CLOROTEKAL must not be given to children or adolescents.

Method of administration
For intrathecal use.
Precautions to take before administering the medicinal product.
The equipment, medicinal products and qualified staff to manage an emergency situation (such as maintaining opening of the respiratory tract and administering oxygen) must be available immediately as occasionally severe reactions, some of which have been fatal, have been described after using local anaesthetics even if the patient had no individual past history of hypersensitivity.

CLOROTEKAL should be injected into the L2/L3, L3/L4 and L4/L5 intervertebral spaces.
Inject the whole dose slowly and check the patient's vital functions very carefully keeping continuous verbal contact with the patient.

As a general guide, follow the points below:
1. use the lowest possible dose
2. administer the substance slowly after drawing up a minimal amount of cerebrospinal fluid to ensure that the needle is correctly positioned
3. do not puncture if signs of skin infection or inflammation are present
4. spinal or intrathecal anaesthesia must not be performed in patients receiving anti-coagulants or those with a congenital or acquired coagulation abnormality.

05 THERAPEUTIC NEED

The indications for spinal anaesthesia (intrathecal injection of local anaesthetics) are subumbilical visceral and lower limb orthopaedic and vascular surgeries carried out over a time compatible with the length of spinal anaesthesia. Local anaesthetics block neuronal conduction in the spinal cord.
Only local anaesthetics with MA for spinal anaesthesia may be injected in clinical practice. These local anaesthetics which can be administered intrathecally are bupivacaine, ropivacaine, and levobupivacaine. These are the only three local anaesthetics which have MA for intrathecal injection. All three of these anaesthetics are long acting.
Chloroprocaine has a short length of action.

06 CLINICALLY RELEVANT COMPARATORS

The similar medicinal products are three local anaesthetics accredited for hospital use. The actual benefit is substantial.

NAME INN *Company*	Date of opinion	IAB (Wording)
Bupivacaine (Bupivacaïne Aguettant, B Braun and Mylan) *Aguettant, B Braun and Mylan*	Not available	Not available
Chirocaine (Levobupivacaine) *Abbott*	08 December 2004	Levobupivacaine does not provide an improvement in actual benefit in its different indications in adults and children compared to bupivacaine and to ropivacaine.
Naropeine (Ropivacaine) *AstraZeneca*	08 June 2005	NAROPEINE 5 mg/ml does not provide an improvement in actual benefit (IAB V) compared with proprietary medicinal products containing bupivacaine and levobupivacaine for the same indications.*

* the only dose indicated for intrathecal use.

Bupivacaine is indicated for use in spinal anaesthesia before surgical procedures suitable for this type of anaesthesia: lower limb surgery, endoscopic or abdominal urological surgery, gynaecological surgery, caesarean sections and sub-umbilical abdominal surgery.

Levobupivacaine is indicated for use in adults in the following situations:
- Surgical anaesthesia:
- Major: peridural (including caesarean), intrathecal, peripheral nerve block.
- Minor: local infiltration, periorbita block in ophthalmic surgery.
- Treatment of pain: continuous peridural infusion or single or repeated bolus administration to treat pain (particularly post operative or childbirth pain).
- In children: for analgesia by infiltration (ilio-inguinal/ilio-hypogastric blocks).

Ropivacaine is indicated for use in spinal anaesthesia (intrathecal) before surgery.

◗ Conclusion

The comparators listed are all clinically relevant.

07 ANALYSIS OF AVAILABLE DATA

07.1 Efficacy

The company provided the results of one phase II study and one phase III study evaluating chloroprocaine against bupivacaine (the pivotal study for the MA file) together with the publication of a study which also compared these two substances.

The phase II study was a dose-finding study, the data from which do not allow an estimate to be made of the magnitude of the effect of chloroprocaine compared with placebo or with an active comparator. This study will not therefore be described.

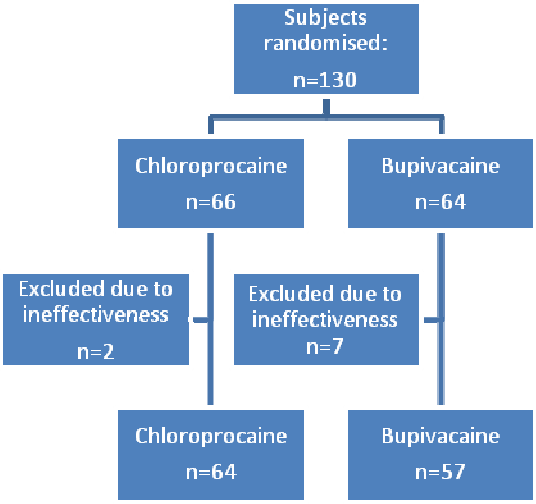
7.1.1 Pivotal study

This currently unpublished study evaluated non-inferiority of chloroprocaine 1% (50 mg) against bupivacaine 0.5% (10 mg).

	Design of the study
Methodology	Single blind, randomised, multi-centre, comparative non-inferiority study in two parallel groups
Study population	Adults between 18 and 80 years old with planned lower abdominal surgery lasting less than 40 minutes
Objective	To evaluate the non-inferiority of 50 mg of chloroprocaine compared with 10 mg of bupivacaine by intrathecal anaesthesia.
Inclusion criteria	From 18 to 80 years old Patients planned for lower abdominal surgery (gynaecological or urological) lasting less than 40 minutes which requires sensory block; Physical condition: ASA physical status I-II
The non-inclusion criteria included	Patients requiring additional anaesthetics such as inhaled anaesthetic agents High blood pressure, past history of lower limb neuromuscular diseases, hypovolaemia.
Treatment groups	Treatment group 5 ml of chloroprocaine 1% i.e. 50 mg, administered as a single intrathecal dose (n=66) Reference group: 2 ml of bupivacaine 0.5% i.e. 10 mg, administered as a single intrathecal dose (n=64)
Primary efficacy endpoint	Time (in minutes) to achieve of sensory block at level T10 assessed by loss of pinprick sensation.
The secondary endpoints included	Time to onset of motor block. Time before walking without assistance. Eligibility for discharge.
Calculation of the number of people required	A maximum difference of 4 minutes between the study substance and the reference substance in terms of times to onset of anaesthesia was deemed to be the non-inferiority threshold. Assuming normal distributions, the sample size required is 50 patients per group. With a sample size of 50 patients per group a single tailed t test at a probability threshold of 25% will have a power of 80%. Assuming the underlying distributions to be non-normal using a non-parametric test, the number calculated above needs to be increased by 15% (i.e. 15% of 50 patients). As a result, 60 patients per treatment group (i.e. a total of 120 patients) was deemed to be satisfactory for the study.

Results:

Patient distribution:



Nine subjects were excluded from the per protocol analysis because of insufficient anaesthesia compared with the level required by the protocol.

Patient characteristics:

Demographic data

	Chloroprocaine group n=66	Bupivacaine group n=64
Age (years) mean ± standard deviation	45.2 ± 15.9	50.6 ± 15.2
Mean BMI ± standard deviation (kg/m²)	25.1 ± 3.8	25.9 ± 3.3
Sex (% men)	36	58

ASA physical status and reason for surgery

		Chloroprocaine group n=66	Bupivacaine Group n=64
ASA status	I	33	26
	II	33	38
Reason for surgery*	Gastrointestinal disorders	1	1
	Infections and infestations	1	2
	Investigations	12	9
	Injury, poisoning and procedural complications.	0	1
	Musculoskeletal and connective tissue disorders.	3	4
	Neoplasm benign, malignant and unspecified (incl. cysts and polyps)	3	2
	Reproductive system and breast disorders	4	6
	Surgical and medical procedures	42	39

* Medra Classification

The demographics of the groups were similar overall at inclusion (although there were more men in the bupivacaine group compared with the other group). Details were lacking for the majority of reasons for surgery.

Primary endpoint

The mean time between injection and full sensory block at the level of T10 was 7.9 minutes in the chloroprocaine group and 9.4 minutes in the bupivacaine group.

	Chloroprocaine group n=64	Bupivacaine group n=57
Mean time to achieve of sensory block ± standard deviation (in minutes)	7.9 ± 6.0	9.4 ± 6.5
Difference 95%CI (in minutes)	-1.5 [-3.8 ; 0.7]	

Taking account of the non-inferiority threshold of 4 minutes, chloroprocaine 1% at a dose of 50 mg was non-inferior to bupivacaine 0.5% at a dose of 10 mg in terms of the time to achieving sensory block.

Secondary endpoints

Results for the times to achieve motor block, end of anaesthesia, walking without assistance and eligibility for discharge from hospital are shown below:

Mean time in min	Chloroprocaine group n=64	Group Bupivacaine n=57	p
achieve of motor block ± standard deviation	5.7 ± 4.9	7.6 ± 5.9	0.03
before the end of anaesthesia ± standard deviation	109.2 ± 25.7	235.5 ± 63.9	< 0.0001
before walking without assistance ± standard deviation	163.3 ± 74.8	307.4* ± 70.6	< 0.0001
eligibility for discharge from hospital. ± standard deviation	190.3 ± 95.4	324.1* ± 77.2	< 0.0001

* missing data for one subject

The times before the end of anaesthesia, walking without assistance and eligibility for discharge from hospital were approximately 2 hours shorter for subjects in the chloroprocaine group compared with the bupivacaine group.

Conclusion

This study demonstrated chloroprocaine to be non-inferior to bupivacaine in terms of the time to achieve of sensory block.

The time to achieve of motor block was shorter in the chloroprocaine group than in the bupivacaine group (a difference of approximately 2 minutes). The time before walking without assistance and time until eligible discharge from hospital was shorter in the subjects in the chloroprocaine group compared with those in the bupivacaine group although this difference of approximately 2 hours is of debatable clinical relevance for either care staff or the patient.

7.1.2 Lacasse study[1]

This study evaluated the efficacy of chloroprocaine 2% (40 mg) compared with bupivacaine 0.75% (7.5 mg).

	Design of the study
Methodology	Double-blind, randomised, single centre, superiority study in two parallel groups
Study population	Adults aged 18 years old and over planned for abdominal surgery lasting less than 60 minutes
Objective	To evaluate the superiority of 40 mg of chloroprocaine against 7.5 mg of bupivacaine given as intrathecal anaesthesia.
Inclusion criteria	Patients aged 18 year old and older Patients planned for abdominal surgery lasting less than 60 minutes. The following types of surgery were included: urological (cystoscopy, circumcision, trans-urethral resection of bladder tumour, hydrocelectomy and varicocelectomy), general surgeries (haemorhoidectomy, rectal biopsy or short ano-rectal surgery) and gynaecological (hysteroscopy, vaginal or vulval biopsy cystocele repair, dilatation and curettage).
The non-inclusion criteria included	INR (International Normalized Ratio) > 1,3, Concomitant anticoagulation, Neurological disorders such as multiple sclerosis, Fluid restriction (renal or heart failure), Allergy or intolerance to local anaesthetics.
Treatment groups	Treatment group: 2 ml of chloroprocaine 2% i.e. 40 mg, administered as a single intrathecal dose (n=53) Reference group: 1 ml of bupivacaine 0.75% i.e. 7.5 mg, administered as a single intrathecal dose (n=53)
Primary endpoint	Time to eligibility for discharge from hospital measured as the time between the intrathecal injection and achieving the criteria for discharge*
The secondary endpoints included	Time to obtain anaesthesia. Length of stay in the recovery room. Time to ambulation. Time to micturition.
Calculation of the number of people required	Calculation of sample size based on: - mean time to discharge from hospital 363 (± 95) min in a study using 7.5 mg of bupivacaine - two-tailed test with significance threshold of 5% and a power of 90% - hypothesis that the length of stay is reduced by 60 minutes in favour of chloroprocaine. As a result, 53 patients were required per group.

*The criteria for discharge were defined by meeting all of the following criteria: complete regression of the sensory block demonstrated by light touch, ability to void, ability to walk, no

[1] Lacasse MA, Roy JD, Forget J et al. Comparison of bupivacaine and 2-chloroprocaine for spinal anaesthesia for outpatient surgery: a double-blind randomised trial. Can J Anaesth 2011;58(4): 384-391

nausea, pain controlled with oral treatment (last dose at least 1 hour before discharge from hospital) and able to tolerate liquids by mouth.

Results:

Patient distribution
A total of 106 patients were randomised (53 per group). No patients were excluded from the study. No patients were lost to follow-up.

Patient characteristics:

Demographic data

	Chloroprocaine group n=53	Bupivacaine group n=53
Age (years) mean ± standard deviation	53 ± 16	54 ± 16
Sex (% men)	45	38

ASA physical status and type of surgery

		Chloroprocaine group n=53	Bupivacaine group n=53
ASA status	I	19	23
	II	32	29
	III	2	1
Type of surgery	Genito-urinary	32	31
	General	12	13
	Gynaecologic	9	9

Overall the groups were similar at inclusion in terms of demographics and type of surgery

Primary endpoint
The mean time to eligibility for discharge from hospital was 277 minutes in the chloroprocaine group and 353 minutes in the bupivacaine group, i.e. a statistically significant difference of 76 minutes ($p<0.001$).

	Chloroprocaine group n=53	Bupivacaine group n=53
The mean time to eligibility from hospital ± standard deviation (in minutes)	277 ± 87	353 ± 99
Difference 95%CI (in minutes)	76 [40; 112]	

2% chloroprocaine at a dose of 40 mg reduced the mean time to eligibility for discharge from hospital compared with 2% bupivacaine at a dose of 7.5 mg. The 76 minutes reduction found is of little clinical relevance.

Secondary endpoints

Mean time in min	Chloroprocaine group n=53	Bupivacaine group n=53	p
to obtain anaesthesia ± standard deviation	6 ± 4	6 ± 3	NS
Mean length of stay in recovery room ± standard deviation	67 ± 16	68 ± 14	NS
to ambulation ± standard deviation	225 ± 56	265 ± 65	0.001
to micturition ± standard deviation	271 ± 96	338 ± 99	0.001

No significant difference was found between the two groups in terms of the time to obtain anaesthesia or length of stay in the recovery room. On the other hand, the time to ambulation was 40 minutes shorter in the chloroprocaine group than in the bupivacaine group Similarly, the time to micturition was approximately 1 hour shorter in the chloroprocaine group compared with the bupivacaine group.

Conclusion

This study showed a 76 minutes mean reduction in the average time to eligibility for discharge from hospital (primary endpoint) for chloroprocaine compared with bupivacaine. This reduction is of little clinical relevance.

A reduction was also seen in the time to ambulation (40 minutes) and to micturition (approximately 1 hour). However, the time to obtain anaesthesia and length of stay in the recovery room were not different between the two groups.

07.2 Adverse effects

7.2.1 Data from clinical studies

Pivotal study

16 patients had at least one adverse events in the pivotal study:

- 7 patients in the chloroprocaine group described 7 adverse events, 4 of which were deemed to be related to treatment;
- 9 patients in the bupivacaine group described 13 adverse events, 10 of which were deemed to be related to treatment.

	Chloroprocaine group n=66		Bupivacaine group n=64	
	Adverse events	Related adverse events	Adverse events	Related adverse events
Bradycardia			1	1
Vomiting			1	
Injection site pain			2	2
Pain			1	1
Anaesthetic complication	1	1	3	3
Foreign body trauma			1	
Transurethral resection syndrome			1	
Hyperglycaemia	1			
Muscle spasms			1	1
Headache	1		1	1
Hypotension	4	3	1	1

Three serious adverse events were reported in the chloroprocaine group: Quincke's oedema before administration of the study treatment, the presence of a fragment of an instrument following the first procedure requiring a second procedure and post-transurethral resection syndrome. None of the serious adverse events was deemed to be related to the study treatment.

Lacasse study
The adverse events reported during surgery and in the recovery room are shown in the table below:

Adverse event	Chloroprocaine group n=53	Bupivacaine group n=53
During the surgery		
Bradycardia	3	4
Hypotension	4	2
Pain requiring analgesia (fentanyl)	10	5
In the recovery room		
Bradycardia	0	2
Hypotension	3	1
Post-operative nausea and vomiting	2	2
Pain requiring analgesia (fentanyl)	13	3

Fewer cases of bradycardia and more cases of hypotension were seen in the chloroprocaine group.
In the recovery room, approximately 4 times more cases of pain were reported in the chloroprocaine group than in the bupivacaine group.
No serious adverse events were reported.

7.2.2 Data from the SPC
According to the SPC, the adverse effects are generally similar to those of the other local anaesthetics (bupivacaine, levobupivacaine, ropivacaine) in intrathecal anaesthesia.
The adverse effects of the medicinal product are difficult to distinguish from the physiological effects of the block itself (such as reduced blood pressure, bradycardia, transient urinary retention), direct effects (such as spinal haematoma) or indirect effects (such as meningitis) of the injection or effects due to loss of cerebrospinal fluid (such as headaches after intrathecal anaesthesia).

07.3 Summary & discussion

One single blind, randomised, non-inferiority study has compared chloroprocaine (50 mg) to bupivacaine (10 mg) by intrathecal administration in 130 adults due to undergo abdominal surgery (gynaecological or urological) lasting less than 40 minutes. Chloroprocaine was shown to be non-inferior to bupivacaine in terms of the time to achieve of a sensory block (primary endpoint). The time to achieve of motor block was shorter in the chloroprocaine group than in the bupivacaine group (a difference of approximately 2 minutes).
The time before walking without assistance and eligibility for discharge from hospital were shorter (approximately 2 hours) for chloroprocaine compared with bupivacaine although these differences are of debatable clinical relevance.

One double blind, randomised, superiority study (Lacasse) has compared chloroprocaine (40 mg) to bupivacaine (7.5 mg) administered intrathecally to 106 adults due to undergo abdominal surgery lasting less than 60 minutes. This showed a small reduction (76 minutes) in the mean time to eligibility for discharge from hospital (primary endpoint), a reduction in the time to ambulation (40 minutes) and in the time to micturition (approximately 1 hour) in the chloroprocaine group of subjects compared with those in the bupivacaine group. These results are clinically of little relevance.

The adverse events reported in both studies were uncommon. In particular these were hypotension and bradycardia.In one study however (Lacasse), approximately 4 times more cases of patients reported pain requiring fentanyl administration in the chloroprocaine group than in the bupivacaine group (13/53 compared with 3/53). According to the SPC these are similar to those of the other local anaesthetics. The adverse effects of chloroprocaine are difficult to distinguish, particularly from the effects of the block itself (hypotension, bradycardia, urinary retention).

08 THERAPEUTIC USE

Intrathecal anaesthesia (spinal anaesthesia[2]) involves injecting an anaesthetic solution into the lumbar subarachnoid space in order to produce sensory and motor block of the lower part of the body. It is indicated for use in subumbilical, visceral and lower limb orthopaedic and vascular surgeries intended to be carried out over a time compatible with the length of spinal anaesthesia[3].
This type of anaesthesia allows ambulatory surgery[4].
The kinetics of onset of anaesthesia and recovery from sensory and motor blocks depend on many factors related both to the patient and to the medicinal product used.
Local anaesthetics block neuronal conduction in the spinal cord. This block is sensory and then motor.
Bupivacaine, ropivacaine, levobupivacaine and now chloroprocaine are the only local anaesthetics with MA for intrathecal use.

In view of the results of the clinical studies, CLOROTEKAL is an alternative to the other local anaesthetics in adult patients prior to planned surgery not lasting in excess of 40 minutes and who can receive intrathecal anaesthesia.

09 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all of the above information and following the debate and vote, the Committee recommends:

09.1 Actual benefit

- Spinal anaesthesia is one of the techniques used for ambulatory surgery. This technique prevents pain and at the same time maintains consciousness. The severity of the conditions treated is extremely variable.
- CLOROTEKAL is intended as symptomatic treatment.
- The efficacy/adverse effects ratio for chloroprocaine is high.
- There are treatment alternatives such as proprietary medicinal products containing bupivacaine, ropivacaine or levobupivacaine.
- This is a first-line therapy.

[2] Malinovsky JM, Anesthésie intrathécale, Les Essentiels 2006, 351-364
[3] Spinal blocks in adults. Clinical practice guidelines. SFAR 2006
[4] Toolkit for development of ambulatory surgery Knowledge loop ANAP-HAS. 2012

Public health benefit:
The conditions within the scope of planned surgery not lasting in excess of 40 minutes are extremely variable in severity. Because of the many intrathecal anaesthetics given in France the public health burden is deemed to be moderate.
This indication is not a public health need.

In light of the available information, chloroprocaine is not expected to have any additional impact on the quality of anaesthesia (particularly time to achieve of sensorimotor block). A low impact on patients' quality of life is expected because of the reduction in the time to ambulation. The reduction in the time to eligibility for discharge from the hospital (about 2 hours) does not appear to be sufficiently significant to be able to change health care organisation.

Overall, CLOROTEKAL is not expected to benefit to public health in this indication.

As a result, the Committee has decided:
The medical benefit offered by CLOROTEKAL is high in the MA indication (intrathecal anaesthesia in adults before planned surgery not lasting in excess of 40 minutes).

09.2 Improvement in actual benefit (IAB)

CLOROTEKAL does not provide an improvement in medical benefit (IAB V, non-existent) compared with the other local anaesthetics which can be administered intrathecally for intrathecal anaesthesia in adults before planned surgery not lasting in excess of 40 minutes.

09.3 Target population

The target population for CLOROTEKAL is adult patients due to receive spinal anaesthesia before surgery not lasting in excess of 40 minutes.
The procedures which involve spinal anaesthesia are orthopaedic surgery, lower limb surgery, urological surgery and sub-umbilical abdominal surgery.
The number of operations and procedures affected may be estimated from the PMSI database. According to 2012 data, approximately 364,000 surgical procedures using spinal anaesthesia were listed.
The numbers of procedures which were planned and only required anaesthesia for 40 min is not listed.

The **maximum target population is therefore 364,000** patients.

This population is based on the proportion of spinal anaesthesias amongst all of the anaesthesias carried out in France and is therefore liable to change as practices changes.

010 TRANSPARENCY COMMITTEE RECOMMENDATIONS

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