HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

24 July 2013

CLEVIPREX 0.5 mg/ml, emulsion for injection

50 ml in vial, B/10 (CIP: 34009 219 976 7 5)
100 ml in vial, B/10 (CIP: 34009 219 977 3 6)

Applicant: THE MEDICINES COMPANY

INN	clevidipine
ATC Code (2012)	C08CA16 (dihydropyridine derivative)
Reason for the request	**Inclusion**
List(s) concerned	**Hospital use** (French Public Health Code L.5123-2)
Indication(s) concerned	**"CLEVIPREX is indicated for the rapid reduction of blood pressure in the perioperative setting"**

Actual Benefit	**The actual benefit is substantial.**
Improvement in Actual Benefit	**Two randomised, open-label (with independent evaluation) studies that compared clevidipine with sodium nitroprusside in a perioperative setting and nicardipine in a post operative setting, did not highlight any difference for the primary endpoints, which included the incidence of myocardial infarction, stroke and renal dysfunction. The only difference observed, in favour of clevidipine, was a higher incidence of death from any cause in the nitroprusside group than in the clevidipine group (4.7% versus 1.7%, p=0.04). However, the use of nitroprusside was not found to be an independent factor associated with an increase in mortality in the multivariate analysis. In maintaining blood pressure within a predefined range (which was only a secondary endpoint), clevidipine was more effective than nitroprusside, but there was no difference highlighted versus nicardipine.** **CLEVIPREX does not provide an improvement in actual benefit (IAB V, non-existent) compared with the two clinically relevant comparators, sodium nitroprusside and nicardipine, in the rapid reduction of blood pressure in a perioperative setting.**
Therapeutic use	**CLEVIPREX is a first-line treatment for the rapid reduction of blood pressure in a perioperative setting.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Initial date (decentralised procedure): 25 July 2012 Risk management plan including the monitoring of "significant" risks (see 08.2 Adverse effects)
Prescribing and dispensing conditions / special status	List I Medicinal product for hospital use only

ATC Classification	2012	
	C:	Cardiovascular system
	C08:	Calcium channel blockers
	C08C:	Selective calcium channel blockers with mainly vascular effects
	C08CA:	Dihydropyridine derivatives
	C08CA16:	Clevidipine

02 BACKGROUND

The applicant is requesting the inclusion of CLEVIPREX 0.5 mg/ml solution for injection, which has clevidipine as the active ingredient, a medicinal product for hospital use only, on the list of medicines approved for hospital use.

Clevidipine is an L type calcium channel blocker from the dihydropyridine category. Type L calcium channel blockers are mediators of the flow of calcium during depolarisation in the smooth arterial muscle. Clevidipine does not reduce the heart refill pressure (inflation pressure), which confirms the absence of effects on the capacitance blood vessels.

03 THERAPEUTIC INDICATIONS

"CLEVIPREX is indicated for the rapid reduction of blood pressure in the perioperative setting."

04 DOSAGE

"Adults/Elderly

Clevidipine is intended for intravenous use.

The dose should be increased progressively to achieve the desired blood pressure reduction. Individualise the dosage depending on the blood pressure to be obtained and the response of the patient.

Blood pressure and heart rate must be monitored continually during the infusion, and then until vital signs are stable.

Patients who receive prolonged clevidipine infusions and are not transitioned to other antihypertensive therapies should be monitored for the possibility of rebound hypertension for at least 8 hours after infusion is stopped.

Initial dose: Initiate the intravenous infusion of clevidipine at 4 ml/h (2 mg/h); the dose may be doubled every 90 seconds. Continue to increase the dose until desired target range is achieved.

Maintenance dose: The desired therapeutic response for most patients occurs at doses of 8 - 12 ml/h (4-6 mg/h).

Maximum dose: Most patients in clinical studies were treated with doses of 32 ml/h (16 mg/h) or less. The maximum recommended dose is 64 ml/h (32 mg/h). There is limited clinical experience in doses over 64 ml/h (32 mg/h). No more than 1000 ml of clevidipine infusion is recommended in the initial 24-hour period due to the associated lipid load. There is limited experience with clevidipine infusion durations beyond 72 hours at any dose.

Transition to an oral antihypertensive agent: Discontinue clevidipine or titrate downward while appropriate oral therapy is established. When an oral antihypertensive agent is being instituted, consider the lag time of onset of the oral agent's effect. Continue blood pressure monitoring until desired effect is achieved. Discontinuation of CLEVIPREX leads to a reduction in antihypertensive effects within 5 to 15 minutes."

05 THERAPEUTIC NEED

Acute perioperative arterial hypertension affect patients undergoing elective or emergency surgical procedures under general anaesthetic and presenting with a drastic, often significant, increase in blood pressure.

Some patients, normal before the procedure, can have an acute perioperative hypertensive crisis associated with multiple factors, such as variations in volume and changes to sympathetic tone as the result of stimulation during surgery, stress or pain. Other factors linked to the anaesthetic may also result in pressure instability. Inhaled or intravenous anaesthetic agents can have a dose-dependant effect on cardiac function by reducing the central sympathetic tone and baroreflex activity, or through direct effects on the myocardium and peripheral blood vessels. Pressure instability may be worsened with positive pressure mechanical ventilation.

In the absence of treatment, acute perioperative arterial hypertension can be responsible for severe sequelae associated with a cerebral, vascular, cardiac or renal risk, that may lead to stroke, aortic dissection, myocardial infarction, haemorrhagic accidents, acute renal impairment or even death. The risk associated with uncontrolled perioperative hypertension depends on the type of surgery, but appears to be more significant within the context of cardiovascular or neurosurgery.[1]

[1] Van den Born BJ, Beutler JJ, Gaillard CA, de Gooijer A, van den Meiracker AH, Kroon AA. Dutch guideline for the management of hypertensive crisis - 2010 revision. Neth J Med 2011; 69: 248-55.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

NAME (INN) *Company*	Indications	Reimbursement
Selective beta-blockers		
BREVIBLOC (Esmolol) *Baxter*	Treatment of supraventricular rhythm disorders: tachycardia, atrial fibrillation or atrial flutter and junctional tachycardia for circumstances where a very short action-time beta-blocker is judged as necessary. During anaesthesia: supraventricular tachyarrhythmia and **hypertension during perioperative period.**	For hospital use
Alpha- and Beta -blockers		
TRANDATE (Labetalol) *Genopharm*	Hypertension with visceral involvement resulting in a very short-term life-threatening prognosis (hypertensive emergency), in particular during: - malignant HTN (with stage III hypertensive retinopathy). - hypertensive encephalopathy. - aortic resection. - left ventricular decompensation with pulmonary oedema. - some serious pre-eclampsia, which is life-threatening to the mother. During anaesthesia: - controlled hypotension. - **hypertension during perioperative period**.	For hospital use
Dihydropyridine derivatives (same TC* as clevidipine)		
LOXEN (Nicardipine) *Novartis Pharma*	Hypertension with visceral involvement resulting in a very short-term life-threatening prognosis (hypertensive emergency), in particular during: - malignant HTN (with stage III hypertensive retinopathy). - hypertensive encephalopathy, - aortic resection, - left ventricular decompensation with pulmonary oedema, - some serious pre-eclampsia, which is life-threatening to the mother. During anaesthesia: - controlled hypotension, - **hypertension during perioperative period**.	For hospital use
Antiadrenergic agents, peripherally acting		
NITRIATE (Nitroprusside) *Serb*	Hypertension with visceral involvement resulting in a very short-term life-threatening prognosis (hypertensive emergency), in particular during: - malignant HTN (with stage III hypertensive retinopathy). - hypertensive encephalopathy, - aortic resection, - left ventricular decompensation with pulmonary oedema. During anaesthesia: - controlled hypotension, **- hypertension during perioperative period**. In cardiology: for some acute heart failure, in particular to the left ventricle, with low heart flow and refractory elevated peripheral resistance, in particular during: - myocardial infarction, - cardiomyopathy, - mitral and aortic valve dysfunction, - and during coronary or valve surgery.	For hospital use

NAME (INN) *Company*	Indications	Reimbursement
Alpha-blockers		
EUPRESSYL (Urapidil) *Nycomed*	Hypertension with visceral involvement resulting in a very short-term life-threatening prognosis (hypertensive emergency), in particular during: - malignant HTN (with stage III hypertensive retinopathy), - hypertensive encephalopathy, - aortic resection, - left ventricular decompensation with pulmonary oedema. During anaesthesia: - controlled hypotension, - **hypertension during perioperative period.**	For hospital use

*TC: therapeutic category

06.2 Other health technologies

Not applicable.

Conclusion

All comparators cited are clinically relevant.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Marketing Authorisation:

Country	Marketing Authorisation	
	Date	Indication
United States	01/08/2008	Reduction in blood pressure when oral treatment is not feasible or not desirable
New Zealand	30/07/2009	Reduction in blood pressure when anticipated and rapid control is desirable
Australia	09/04/2010	Short-term reduction in blood pressure when oral treatment is not feasible or not desirable
Switzerland	11/07/2010	Rapid reduction of blood pressure in perioperative situations
Canada	15/04/2011	Treatment of acute elevations in blood pressure
United Kingdom	23/11/2011	Rapid reduction of blood pressure in perioperative situations
Holland	30/11/2011	Rapid reduction of blood pressure in perioperative situations
Sweden	20/01/2012	Rapid reduction of blood pressure in perioperative situations
Germany	18/04/2012	Rapid reduction of blood pressure in perioperative situations
Austria	12/07/2012	Rapid reduction of blood pressure in perioperative situations
Belgium	19/11/2012	Rapid reduction of blood pressure in perioperative situations

Reimbursement abroad:

CLEVIPREX is available in hospitals in the United States. CLEVIPREX is not subject to specific reimbursement (global negotiation).

In Germany, a request for exemption from reimbursement assessments was accepted by the authorities on 22 November 2012, as CLEVIPREX is a product that is for hospital use only.

There are no other assessments for reimbursement in progress.

08 ANALYSIS OF THE AVAILABLE DATA

The applicant has provided 5 clinical studies carried out on clevidipine in the rapid reduction of blood pressure in a perioperative setting:

- Two randomised, placebo-controlled, double-blind studies of patients undergoing cardiac surgery with the aim of comparing the failure rate (defined by the absence of a reduction in blood pressure or an inadequate reduction or intolerance) of clevidipine compared with placebo in a preoperative setting (ESCAPE-1 study)[2] or in a postoperative setting (ESCAPE-2 study).[3]

- Three open-label randomised, active comparator-controlled studies (nitroglyrecin or nitroprusside or nicardipine), in patients undergoing cardiac surgery.[4]
It should be noted that there is no nitroglyrecin -based proprietary medicinal product indicated for the reduction of blood pressure in a perioperative setting available in France. NITRONAL 1 mg/ml (nitroglyrecin) solution for infusion is indicated in the prevention of myocardial ischaemia during cardiac surgery, for left ventricular failure, especially during the acute phase of myocardial infarction, and for unstable angina.

The primary aim of these three studies was to compare the incidence of death from any cause, myocardial infarction, stroke (ischaemic or haemorrhagic) and renal dysfunction with clevidipine compared with an active comparator. The secondary aim was to compare the control of blood pressure with clevidipine with each of the three active comparators.

Other studies presented by the applicant:
Two non-comparative studies also evaluated the efficacy and safety of clevidipine in non-surgical settings, one in the context of persistent, severe HTN with or without visceral involvement, in the emergency department or intensive care unit (VELOCITY study)[5] and the other on patients with intracerebral haemorrhage (ACCELERATE study).[6] The results from these studies are not taken into account within the context of this assessment due to the fact they were open-label, non-comparative studies carried out on off-list indications for CLEVIPREX.

[2] Levy JH, Mancao MY, Gitter R, Kereiakes DJ, Grigore AM, Aronson S, Newman MF. Clevidipine effectively and rapidly controls blood pressure preoperatively in cardiac surgery patients: the results of the randomized, placebo-controlled efficacy study of clevidipine assessing its preoperative antihypertensive effect in cardiac surgery-1. Anesth Analg 2007;105:918-25
[3] Singla N, Warltier DC, Gandhi SD, Lumb PD, Sladen RN, Aronson S, Newman MF, Corwin HL; ESCAPE-2 Study Group. Treatment of acute postoperative hypertension in cardiac surgery patients: an efficacy study of clevidipine assessing its postoperative antihypertensive effect in cardiac surgery-2 (ESCAPE-2), a randomized, double-blind, placebo-controlled trial. Anesth Analg 2008;107:59-67.
[4] Aronson S, Dyke CM, Stierer KA, Levy JH, Cheung AT, Lumb PD, Kereiakes DJ, Newman MF. The ECLIPSE trials: comparative studies of clevidipine to nitroglycerin, sodium nitroprusside, and nicardipine for acute hypertension treatment in cardiac surgery patients. Anesth Analg 2008;107:1110-21.
[5] Pollack CV, Varon J, Garrison NA, Ebrahimi R, Dunbar L, Peacock WF 4th. Clevidipine, an intravenous dihydropyridine calcium channel blocker, is safe and effective for the treatment of patients with acute severe hypertension. Ann Emerg Med 2009; 53:329-38.
[6] Graffagnino C, Bergese S, Love J, Schneider D, Lazaridis C, LaPointe M, Lee K, Lynch G. Aggressive Blood Pressure Control with Clevidipine in Patients with Acute Intracerebral Hemorrhage is Rapid and Well Tolerated: The ACCELERATE Trial. Stroke 2011;42: e218, abstract no. WP206.

08.1 Efficacy

8.1.1 Placebo-controlled studies

	ESCAPE-1	ESCAPE-2
Primary study objective	Demonstrate the efficacy of CLEVIPREX compared with placebo	
Method	Randomised, placebo-controlled, double-blind, parallel groups, multicentre	
Main inclusion criteria	Pre-randomisation: Age >18 years, scheduled for heart surgery (coronary artery bypass graft and/or valve surgery with or without cardiopulmonary bypass)	
	HTN in the previous 6 months or currently Post-randomisation: • Preoperative SBP ≥160 mmHg, after introduction of an arterial catheter • Need for reduction in SBP ≥15%	Post-randomisation • Postoperative SBP ≥140 mmHg at 4 hours • Need for reduction in SBP ≥15%
Main non-inclusion criteria	• Stroke in the previous 3 months • Pre-existing left branch block or permanent ventricular pacing • Known intolerance to dihydropyridines • Soya or egg allergy	
Treatment groups	The initial dosage of clevidipine was 0.4 µg/kg/min (approximately 2 mg/h for an adult weighing 80 kg), doubled every 90 seconds to 3.2 µg/kg/min, with a maximum dose of 8.0 µg/kg/min. The administration time was at least 30 minutes (except in cases of treatment failure) and a maximum of one hour (or until anaesthesia was started in the ESCAPE-1 study). The placebo corresponded to a CLEVIPREX lipid emulsion.	
Primary efficacy endpoint	Treatment failure rate in the 30 minutes following the start of treatment, defined as a premature and definitive discontinuation of treatment motivated by: • An absence in efficacy (blood pressure unchanged or increased or impossibility of achieving a reduction in blood pressure) • A treatment failure: non-achievement in a reduction ≥15% in SBP in 30 minutes • An intolerance to treatment	
Secondary endpoints included	• Time to achieve a reduction ≥15% in SBP • Variation in mean BP compared with baseline	
Randomisation	Centralised (IVRS), blocks of 4 per centre	
Calculation on the number of participants	Hypothesis of a 40% success rate in the clevidipine group and 12% in the placebo group: 50 patients per treatment group for a power of 85% and a bilateral statistical significance of 0.05.	Hypothesis of a failure rate of <60% with clevidipine and 88% with placebo: 50 patients per treatment group for a power of 85% and a bilateral statistical significance of 0.05.
Statistical analysis	The intention to treat (ITT) analysis population included all randomised patients regardless of the treatment effectively received. The safety analysis population included all randomised and treated patients.	

Results:

- **In the treatment of preoperative hypertension (ESCAPE-1)**

A total of 76 patients were randomised in each group. A total of 23 patients in the clevidipine group and 24 patients in the placebo group did not meet post-randomisation inclusion criteria. One patient in the placebo group did not receive the treatment as planned. The efficacy analysis population is therefore based on 53 patients in the clevidipine group and 52 in the placebo group. The safety analysis population is based on 53 patients in the clevidipine group and 51 in the placebo group.

The patient characteristics were comparable between the two groups, except for a higher proportion of elderly patients, patients with a history of myocardial infarction and a lower proportion

of patients with a family history of heart disease in the clevidipine group compared with the placebo group (Table 1).

- **In the treatment of postoperative hypertension (ESCAPE-2)**

A total of 206 patients were randomised: 100 in the clevidipine group and 106 in the placebo group. A total of 61 patients from the clevidipine group and 49 patients from the placebo group met post-randomisation inclusion criteria (efficacy analysis population). The safety analysis population was identical to that of the efficacy analysis population.

The patient characteristics were comparable between the two groups, except for a higher proportion of elderly patients and a lower proportion of patients with a history of angina in the clevidipine group compared with the placebo group (Table 1).

Table 1: Main baseline patient characteristics - Placebo-controlled studies

	ESCAPE-1 Preoperative setting		**ESCAPE-2 Postoperative setting**	
	Clevidipine N=53	**Placebo N=52**	**Clevidipine N=61**	**Placebo N=49**
Age, mean ± SD (years)	65.8±10.0	61.7±10.3*	63.8±12.6	62.3±11.8
Age ≥65, n (%)	33 (62.3)	8 (34.6)*	33 (54.1)	17 (34.7)*
Gender male, n (%)	37 (69.8)	36 (69.2)	47 (77.0)	38 (77.6)
Hypertension, n (%)	53 (100.0)	52 (100.0)	51 (83.6)	41 (83.7)
History of stroke, n (%)	3 (5.7)	2 (3.8)	4 (6.6)	4 (8.2)
Heart failure, n (%)	6 (11.3)	6 (11.5)	12 (19.7)	5 (10.2)
Diabetes, n (%)	19 (35.8)	25 (48.1)	21 (34.4)	17 (34.7)
History of myocardial infarction, n (%)	16 (30.2)	6 (11.5)*	15 (24.6)	15 (30.6)
History of coronary artery bypass graft, n (%)	5 (9.4)	1 (1.9)	1 (1.6)	2 (4.1)
Angina, n (%)	34 (64.2)	30 (57.7)	26 (42.6)	31 (63.3)*
Family history of heart disease, n (%)	27 (50.9)	40 (76.9)*	29 (47.5)	27 (55.1)
Initial systolic blood pressure, mean ± SD (mmHg)	182±22	177±19	147.4±8.4	150.5±11.8

*SD: standard deviation. *p<0.05.*

In the study in a preoperative setting, 7 patients from each group received a beta-blocker on the day of surgery, before starting the study treatment. During the administration of the study treatment, a higher number of patients in the placebo group received nitroglyrecin (17.3% which is 9 patients and 1.9% which is 1 patient in the clevidipine group).

In the study in a postoperative setting, a higher proportion of patients from the clevidipine group received a beta-blocker or a vasodilator before starting the study treatment. A higher proportion of patients in the placebo group received treatment with a beta-blocker or a vasodilator during administration of the study treatment (Table 2).

Table 2: Perioperative treatments – ESCAPE-2 study

	Before the start of the study treatment		During administration of the study treatment	
	Clevidipine N=61 n (%)	Placebo N=49 n (%)	Clevidipine N=61 n (%)	Placebo N=49 n (%)
Patients receiving at least one beta-blocker/ vasodilator	37 (60.7)	20 (40.8)	25 (41.0)	36 (73.5)

Results for the primary efficacy endpoint

A significant difference in favour of clevidipine was highlighted compared with placebo in terms of treatment failure rate (Table 3):

- 7.5% in the placebo group versus 82.7% in the clevidipine group (95% CI: 62.64% to 87.65%, p<0.0001) in the study in the preoperative setting,
- 8.2% in the placebo group versus 79.6% in the clevidipine group (95% CI: 58.18% to 84.61%, p<0.0001) in the study in the postoperative setting.

Results for the secondary endpoints

Clevidipine enabled a reduction in systolic BP ≥15% compared with baseline values in a median time of 6 minutes in the preoperative setting and 5.3 minutes in the postoperative setting (Table 3).

In the study in the preoperative setting, a higher statistically significant reduction in mean blood pressure was observed in the CLEVIPREX group from the 5th minute and every 5 minutes to the end of the 30 minute treatment period. For the lowest mean BP, the mean reduction was -34.8 mmHg (-31.2%) in the CLEVIPREX group and -12.5 mmHg (-11.2%) in the placebo group (p<0.0001).

In the study in the postoperative setting, a higher statistically significant reduction in mean BP was observed in the CLEVIPREX group from the 2nd minute, with a mean reduction of -5.7 mmHg (-5.9%) *vs*. -0.1 mmHg (-0.1%; p=0.0004), and this difference in favour of CLEVIPREX remained statistically higher at 5, 10 and 15 minutes after the start of treatment. For the lowest mean BP, the mean reduction was -28.1 mmHg (-28.9%) in the CLEVIPREX group and -8.9 mmHg (-8.7%) in the placebo group (p<0.0001).

Table 3: Efficacy results for clevidipine versus placebo

	ESCAPE-1 Preoperative setting			ESCAPE-2 Postoperative setting		
	Clevidipine N=53	Placebo N=52	p[a]	Clevidipine N=61	Placebo N=49	p[a]
Primary efficacy endpoint						
Treatment failure, n (%)	4 (7.5)	43 (82.7)	<0.0001	5 (8.2)	39 (79.6)	<0.0001
Lack of efficacy	0 (0.0)	18 (34.6)	<0.0001	0 (0.0)	37 (75,5)	<0.0001
Insufficient efficacy	4 (7.5)	25 (48.1)	<0.0001	2 (3.3)	2 (4.1)	1.0000
Intolerance	0 (0.0)	0 (0.0)	-	3[c] (4.9)	0 (0.0)	0.2521
Success of treatment, n (%)	49 (92.5)	9 (17.3)	<0.0001	56 (91.8)	10 (20.4)	<0.0001
Secondary endpoints						
Median time (in minutes) to achieve target SBP value[b] (95% CI)	6 (6 to 8)	Not estimated[d]	-	5.3 (4 to 7)	Not estimated[d]	<0.0001

[a]Chi-2 test; [b]Time to achieve a reduction ≥15% compared with baseline value; [c]An episode of atrial fibrillation resolved the same day with no sequelae, and 2 episodes of very significant low pressure in the 1st minutes of treatment; [d]Not estimated due to the number of patients achieving target BP value being too small.

8.1.2 Clevidipine versus active comparator studies

	ECLIPSE-NTG	ECLIPSE-SNP	ECLIPSE-NIC
Primary study objective	Compare the safety of clevidipine versus an active comparator		
	In a preoperative, perioperative and postoperative setting		In a postoperative setting
Comparator	nitroglyrecin	nitroprusside	nicardipine
Method	Randomised, open-label active comparator controlled study (due to the difficult practicalities of comparing two different intravenous regimens and the impossibility of detecting the potential adverse effects linked to the clevidipine lipid emulsion in cases of double placebo (use of INTRALIPID))		
Primary inclusion criteria	Age ≥18 years, scheduled for heart surgery (coronary artery bypass graft and/or valve surgery with or without cardiopulmonary bypass)		
	Requiring treatment for perioperative HTN		Requiring treatment for postoperative HTN
Main non-inclusion criteria	• Stroke in the previous 3 months • Permanent ventricular pacing • Intolerance to calcium channel blockers • Hypersensitivity to nitroglyrecin , nitroprusside or nicardipine • Soya or egg allergy		
Treatment groups	The initial dosage of clevidipine was 0.4 µg/kg/min (approximately 2 mg/h for an adult weighing 80 kg), doubled every 90 seconds to 3.2 µg/kg/min, and a maximum dosage of 8.0 µg/kg/min. Administration of doses ranged from 4.4 to 8.0 µg/kg/min, not exceeding 2 hours. Titration to 8.0 µg/kg/min was required before moving on to, or adding, a new injectable antihypertensive agent. A reduction in dose or a temporary discontinuation of clevidipine was possible, depending on the response of the patient. The comparator was administered at its standard dosage.		
Primary efficacy endpoint	Incidence of death from any cause, myocardial infarction, stroke (ischaemic or haemorrhagic), renal dysfunction (serum creatinine ≥2.0 mg/dl or 177 µmol/l, increase of serum creatinine ≥0.7 mg/dl or 62 µmol/l compared with baseline, and/or requiring haemodialysis or haemofiltration) between the start of treatment and 30 days after surgery. All events were assessed by an independent committee without notifying the treatment groups.		
Secondary endpoints included	Area under the curve (AUC) normalised by the time of deviations in blood pressure outside the predetermined lower and upper limits (135-65 mmHg in perioperative setting and 145-75 mmHg in pre and post operative setting), taking into account the size of the deviation and its duration: AUC_{SBP-D} (mmHg x min/h) between the start of treatment and its end or 24 hours after its start. Use of alternative antihypertensive agents.		
	Measurement of BP every 15 minutes in a preoperative setting, every 5 minutes in a perioperative setting, and, in a postoperative setting, every 15 minutes for 6 hours, then once every hour up to 24 hours.		Every 15 minutes for 6 hours, then once every hour up to 24 hours post surgery.
Calculation of the number of patients needed	There was no calculation of the number of participants or the study power. The number of participants was determined based on clinical experience and in agreement with the FDA.		
	500 to 900 scheduled	250 to 500 scheduled	250 to 500 scheduled
Statistical analysis	The intention to treat (ITT) analysis population included all randomised patients regardless of the treatment effectively received. The safety analysis population included all randomised and treated patients.		

Results:

On inclusion, the patients' characteristics were comparable between the treatment groups, with the exception of there being more hypertensive patients in the clevidipine group compared with the nicardipine group (Table 4).

Table 4: Main baseline patient characteristics - clevidipine versus active comparator studies

	ECLIPSE-NTG		ECLIPSE-SNP		ECLIPSE-NIC	
	Clevidipine n=268	**Nitroglyrecin n=278**	**Clevidipine n=296**	**Nitroprusside n=283**	**Clevidipine n=188**	**Nicardipine n=193**
Age, years	64.4±10.9	63.9±11.1	64.2±10.9	65.3±11.0	66.1±10.1	66.1±10.2
Gender, male	214 (79.9)	207 (74.5)	204 (68.9)	216 (76.3)	126 (67.0)	138 (71.5)
Age ≥65 years	138 (51.5)	138 (49.6)	146 (49.3)	158 (55.8)	103 (54.8)	111 (57.5)
Initial BP, mmHg						
SBP	142.9±22.7	139.1± 28.3	142.1±21.6	141.8±26.1	144.2±19.2	144.0±20.1
DBP	71.9±13.3	71.3±14.7	70.7±13.7	70.7±17.2	69.2±12. 8	68.4±13.0
History						
Hypertension	224 (83.6)	240 (86.3)	253 (85.5)	228 (80.6)	181 (96.3)*	169 (87.6)
Myocardial infarction < 6 months	46 (17.2)	51 (18.3)	46 (15.5)	45 (15.9)	39 (20.7)	42 (21.8)
History of coronary artery bypass graft	10 (3.7)	24 (8.6)	10 (3.4)	11 (3.9)	4 (2.1)	8 (4.1)
Heart failure	35 (13.1)	44 (15.8)	65 (22.0)	52 (18.4)	44 (23.4)	38 (19.7)
Dyslipidaemia	209 (78.0)	193 (69.4)	196 (66.2)	191 (67.5)	134 (71.3)	137 (71.0)
Diabetes	99 (36.9)	92 (33.1)	99 (33.4)	102 (36.0)	68 (36.2)	76 (39.4)
CVA or transient ischaemic attack	37 (13.8)	42 (15.1)	21 (7.1)	18 (6.4)	16 (8.5)	12 (6.2)
Atrial flutter/fibrillation	33 (12.3)	32 (11.5)	48 (16.2)	43 (15.2)	21 (11.2)	21 (10.9)
Antihypertensive treatment in the 2 weeks before surgery						
Beta-blockers	172 (64.2)	192 (69.1)	192 (64.9)	189 (66.8)	132 (70.2)	135 (69.9)
ACE	121 (45.1)	114 (41.0)	134 (45.3)	119 (42.0)	71 (37.8)	79 (40.9)
Calcium inhibitors	52 (19.4)	60 (21.6)	68 (23.0)	60 (21.2)	45 (23.9)	28 (14.5)

Mean ± SD or n (%).

TNT: nitroglyrecin ; NPS: nitroprusside; NIC: nicardipine; SBP: systolic blood pressure; DBP: diastolic blood pressure; CVA: cerebral vascular accident (stroke); ACE: angiotensin-converting enzyme inhibitor

**p<0.05 vs. nicardipine*

The total infusion duration for clevidipine, including the times where the infusion was stopped, was 6.4 hours in the study versus nitroglyrecin , 6.7 hours in the study versus nitroprusside and 7.1 hours in the study versus nicardipine (Table 5). The infusion time, the total infusion volume and the infusion flow rate were all higher in the nitroglyrecin group compared with the clevidipine group, although these three parameters were comparable between both groups in the study versus nitroprusside. The total volume and the infusion flow rate were higher in the nicardipine group than in the clevidipine group.

Table 5: Administration of study treatments - Clevidipine versus active comparator studies

	ECLIPSE-NTG		ECLIPSE-SNP		ECLIPSE-NIC	
	Clevidipine n=268	Nitroglyrecin n=278	Clevidipine n=296	Nitroprusside n=283	Clevidipine n=188	Nicardipine n=193
Start time						
Preoperative setting	92 (34.3)	119 (42.8)	52 (17.6)	34 (12.0)	0 (0.0)	0 (0.0)
Perioperative setting	145 (54.1)	132 (47.5)	161 (54.4)	158 (55.8)	0 (0.0)	0 (0.0)
Postoperative setting	31 (11.6)	27 (9.7)	83 (28.0)	90 (31.8)	188 (100.0)	193 (100.0)
Treatment received in						
Preoperative setting	92 (34.3)	119 (42.8)	52 (17.6)	34 (12.0)	0 (0.0)	0 (0.0)
Perioperative setting	229 (85.4)	245 (88.1)	209 (70.6)	185 (65.4)	0 (0.0)	0 (0.0)
Postoperative setting	187 (69.8)	226 (81.3)	219 (74.0)	204 (72.1)	188 (100.0)	193 (100.0)
Total infusion time, h*	6.4 (2-16)	12.0 (4-24)	6.7 (2-17)	5.4 (2-18)	7.1 (2-17)	7.9 (3-18)
Total infusion volume, ml	21.8 (6.3-74.2)	74.8 (24.1-209.1)	26.5 (7.1-97.1)	25.6 (5.5-129.4)	56.4 (13.7-142.9)	163.8 (42.7-376.2)
Infusion flow rate, ml/h	6.2 (4.4-10.2)	11.3 (6.1-22.7)	6.4 (4.5-10.2)	8.5 (4.1-17.4)	7.9 (4.5-12.9)	33.6 (18.9-48.8)

*Median (Quartile 1 - Quartile 3) or n (%). TNT: nitroglyrecin ; NPS: nitroprusside; NIC: nicardipine. *Including periods when infusion was stopped.*

Results for the primary efficacy endpoint

There was no significant difference highlighted between clevidipine and any of the other comparators (nitroglyrecin , nitroprusside or nicardipine) for the criteria of the occurrence of myocardial infarction, stroke and renal dysfunction between the start of treatment and 30 days after surgery (Table 6).

There was no significant difference highlighted between clevidipine and nitroglyrecin or between clevidipine and nicardipine regarding the incidence of death from any cause.

Only one significantly higher incidence of death from any cause in the nitroprusside group than in the clevidipine group was observed (4.7% versus 1.7%, p=0.04). However, the use of nitroprusside was not found to be an independent factor associated with the increase in mortality in the multivariate analysis. Of the 13 patients who died in the nitroprusside group, three presented with reported hypotension as an adverse event.

Table 6: Primary efficacy endpoint - Events at 30 days - Clevidipine versus active comparator studies

n/N (%)	Clevidipine N=268	Nitroglyrecin N=278	p
Death from any cause	7/252 (2.8)	9/266 (3.4)	NS
Myocardial infarction	8/246 (3.3)	9/260 (3.5)	NS
Stroke	4/245 (1.6)	6/260 (2.3)	NS
Renal dysfunction	17/248 (6.9)	21/260 (8.1)	NS
n/N (%)	**Clevidipine N=296**	**Nitroprusside N=283**	**p**
Death from any cause	5/286 (1.7)	13/274 (4.7)	0.04
Myocardial infarction	4/281 (1.4)	6/264 (2.3)	NS
Stroke	3/282 (1.1)	4/262 (1.5)	NS
Renal dysfunction	24/284 (8.5)	24/265 (9.1)	NS
n/N (%)	**Clevidipine N=188**	**Nicardipine N=193**	**P**
Death from any cause	8/181 (4.4)	6/189 (3.2)	NS
Myocardial infarction	4/173 (2.3)	2/183 (1.1)	NS
Stroke	1/173 (0.6)	2/183 (1.1)	NS
Renal dysfunction	15/180 (8.3)	11/185 (5.9)	NS
n/N (%)	**Clevidipine N=752**	**All comparators N=754**	**P**
Death from any cause	20/719 (2.8)	28/729 (3.8)	NS
Myocardial infarction	16/700 (2.3)	17/707 (2.4)	NS
Stroke	8/700 (1.1)	12/705 (1.7)	NS
Renal dysfunction	56/712 (7.9)	56/710 (7.9)	NS

Secondary endpoint results:

- **Antihypertensive effect**

Maintaining pressure figures within the predefined blood pressure range was significantly superior with:

- clevidipine compared with nitroglyrecin (median AUC_{SBP} 4.14 vs. 8.87 mmHg x min/h, p=0.0006). The AUC_{SBP-D} above the upper threshold value was significantly lower with clevidipine compared with nitroglyrecin (2.76 *vs*. 7.94 mmHg x min/h; p=0.0002). The AUC_{SBP-D} below the lower threshold value was comparable between both groups (zero in both groups).
- clevidipine compared with nitroprusside (median AUC_{SBP} 4.37 vs. 10.50 mmHg x min/h, p=0.0027), as well as for deviations above the upper threshold value (2.70 *vs*. 6.61 mmHg x min/h; p=0.031) than for those below the lower threshold value (2.30 *vs*. 8.38 mmHg x min/h; p=0.0006).

There was no statistically significant difference highlighted in terms of blood pressure control between clevidipine and nicardipine within the context of predefined threshold values.

The percentage of patients who received an alternative injectable antihypertensive treatment was similar between the clevidipine group and the nitroglyrecin group (57.8% versus 56.8%) as well as between the clevidipine group and the nicardipine group (40.4% versus 39.5%), but lower in the clevidipine group than in the nitroprusside group (45.1% versus 55.3%).

- **Heart rate**

A modest increase in heart rate was observed in the 24 hours following the start of treatment, with a median percentage variation between the baseline value and the median of all postoperative values of:

- 31.4% in the clevidipine group and 32.1% in the nitroglyrecin group,
- 26.9% in the clevidipine group and 30.3% in the nitroprusside group

In the study versus nicardipine, no notable increase was observed in heart rate in both treatment groups in the 24 hours following the start of treatments.

Reflex tachycardia was reported in:

- two patients in the clevidipine group (0.7%) and one patient in the nitroglyrecin group (0.4%),
- four patients in the clevidipine group (1.4%) and four patients in the nitroprusside group (1.4%),
- one patient in the clevidipine group (<1%) and no patients in the nicardipine group.

The incidence of supra-ventricular tachycardia was:
- 36.6% in the clevidipine group and 34.9% in the nitroglyrecin group,
- 41.9% in the clevidipine group and 40.6% in the nitroprusside group,
- 41.5% clevidipine group and 37.8% in the nicardipine group.

08.2 Safety/Adverse effects

8.2.1 From clinical studies

- **Clevidipine versus placebo studies**

The incidence of adverse events (AE), of treatment-related adverse events and serious adverse events (SAE) was higher in the clevidipine group compared with the placebo group (Table 7).

Table 7: Adverse events occurring between the start and 7 days after the end of study treatment or discharge from hospital - Clevidipine versus placebo studies

	ESCAPE-1 Preoperative setting		ESCAPE-2 Postoperative setting	
	Clevidipine N=53 n (%)	Placebo N=51 n (%)	Clevidipine N=61 n (%)	Placebo N=49 n (%)
At least one AE	38 (71.7)	33 (64.7)	39 (63.9)	28 (57.1)
At least one study treatment-related AE	5 (9.4)[a]	2 (3.9)[a]	3 (4.9)[a,b]	0 (0.0)
AE leading to discontinuation of the study treatment	1 (1.9)	1 (2.0)	2 (3.3)	0 (0.0)
At least one SAE	13 (24.5)	10 (19.6)	10 (16.4)	6 (12.2)
Death	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)

[a]*Considered as possibly study treatment-related.* [b]*Including two occurring on Day 2 (thrombophlebitis) and Day 6 (insomnia) after the end of treatment with clevidipine.*

In the study in a preoperative setting, one death occurred in the clevidipine group: this death occurred one day after the procedure due to mediastinal haemorrhage and was considered as not related to the study treatment by the investigator.

In the study in a postoperative setting, a single serious adverse event was considered as possibly being related to the study treatment by the investigator: thrombophlebitis occurred two days after the end of the study treatment in the clevidipine group.

For two patients in the clevidipine group, the study treatment was discontinued due to a serious adverse event: one episode of atrial fibrillation considered as a treatment failure due to intolerance and as study treatment-related and one ventricular tachycardia not considered as related to the study treatment.

The most common adverse events (incidence ≥5%) were (Table 8):

Table 8: The most common adverse events (≥5%) - Clevidipine versus placebo studies

	ESCAPE-1 Preoperative setting		**ESCAPE-2 Postoperative setting**	
	Clevidipine N=53 n (%)	**Placebo N=51 n (%)**	**Clevidipine N=61 n (%)**	**Placebo N=49 n (%)**
Patients with at least one AE (incidence ≥5%)	27 (50.9)	21 (41.2)	32 (52.5)	24 (49.0)
Pyrexia	10 (18.9)	7 (13.7)	3 (4.9)	3 (6.1)
Atrial fibrillation	7 (13.2)	6 (11.8)		
Acute renal impairment	5 (9.4)	1 (2.0)		
Anxiety	3 (5.7)	1 (2.0)	5 (8.2)	3 (6.1)
Atelectasia (loss of lung volume)	3 (5.7)	0 (0.0)	2 (3.3)	5 (10.2)
Cough	3 (5.7)	2 (3.9)		
Migraine	3 (5.7)	1 (2.0)		
Hypotension	3 (5.7)	1 (2.0)		
Nausea	3 (5.7)	5 (9.8)	13 (21.3)	6 (12.2)
Pleural effusion	3 (5.7)	4 (7.8)		
Ventricular tachycardia	2 (3.8)	4 (7.8)	4 (6.6)	2 (4.1)
Insomnia			13 (21.3)	6 (12.2)
Constipation			6 (9.8)	3 (6.1)
Oedema			5 (8.2)	6 (12.2)
Anaemia			4 (6.6)	3 (6.1)
Peripheral oedema			4 (6.6)	2 (4.1)
Wheezing			4 (6.6)	2 (4.1)
Confused state			3 (4.9)	4 (8.2)
Complication at the incision site			3 (4.9)	3 (6.1)
Vomiting			2 (3.3)	3 (6.1)
Agitation			1 (1.6)	3 (6.1)
Pulmonary oedema			1 (1.6)	4 (8.2)
Tachycardia			1 (1.6)	4 (8.2)

The most commonly observed adverse events with clevidipine during the placebo-controlled studies were: fever, atrial fibrillation, nausea and insomnia.

An increase in heart rate during the 30 minute treatment period with clevidipine was observed during the study in a preoperative setting but not in the postoperative setting.

In the study in the preoperative setting, the median baseline heart rate was 71 bpm (min-max: 48-120) in the clevidipine group versus 76 bpm (min-max: 53-126) in the placebo group. The median maximum heart rate during the 30 minute treatment period was 84 bpm (min-max: 57-132) in the clevidipine group versus 84 bpm (min-max: 57-133) in the placebo group. No changes in heart rate were observed after stopping treatment in patients who received clevidipine.

In the study in the postoperative setting, the median baseline heart rate was 90 bpm (min-max: 45-142) in the clevidipine group versus 90 bpm (min-max: 67-135) in the placebo group. The median maximum heart rate during the 30 minute treatment period was 93 bpm (min-max: 57-152) in the clevidipine group versus 92 bpm (min-max: 67-150) in the placebo group.

- **Clevidipine versus active comparator studies**

The adverse events observed during the medicine infusion period and up to 7 days thereafter (or discharge from hospital) for patients who received clevidipine and for those who received the active comparators are found in Table 9. The incidence of adverse effects that led to treatment discontinuation was:
- 4.9% in the CLEVIPREX group versus 1.4% in the nitroglyrecin group,
- 2.4% in the CLEVIPREX group versus 2.1% in the nitroprusside group,
- 6.9% in the CLEVIPREX group versus 5.7% in the nicardipine group.

Table 9: Adverse events occurring between the start and 7 days after the end of study treatment or discharge from hospital - Clevidipine versus active comparator studies

	ECLIPSE-NTG		ECLIPSE-SNP		ECLIPSE-NIC	
	Clevidipine N=268	Nitroglyrecin N=278	Clevidipine N=296	Nitroprusside N=283	Clevidipine N=188	Nicardipine N=193
At least one AE	267 (99.6)	278 (100.0)	296 (100.0)	283 (100.0)	187 (99.5)	193 (100.0)
At least one study treatment-related AE	44 (16.4)	25 (9.0)	34 (11.5)	20 (7.1)	36 (19.1)	25 (13.0)
AE leading to discontinuation of the study treatment	13 (4.9)	4 (1.4)	7 (2.4)	6 (2.1)	13 (6.9)	11 (5.7)
At least one SAE	43 (16.0)	51 (18.3)	57 (19.3)	66 (23.3)	33 (17.6)	34 (17.6)

The type of serious adverse event is stated in Table 10.

Table 10: Serious adverse events at Day 30 as a function of the study - Clevidipine versus active comparators

	ECLIPSE-NTG		ECLIPSE-SNP		ECLIPSE-NIC	
	Clevidipine (N=268) n (%)	Nitroglyrecin (N=278) n (%)	Clevidipine (N=296) n (%)	Nitroprusside (N=283) n (%)	Clevidipine (N=188) n (%)	Nicardipine (N=193) n (%)
At least one SAE	43 (16.0)	51 (18.3)	57 (19.3)	66 (23.3)	33 (17.6)	34 (17.6)
SAE†						
Atrial fibrillation	7 (2.6)	7 (2.5)	9 (3.0)	7 (2.5)	2 (1.1)	4 (2.1)
Respiratory failure	3 (1.1)	9 (3.2)	2 (0.7)	7 (2.5)	3 (1.6)	3 (1.6)
Acute renal impairment	9 (3.4)	1 (0.4)	7 (2.4)	8 (2.8)	1 (0.5)	4 (2.1)
Ventricular fibrillation	4 (1.5)	5 (1.8)	2 (0.7)	5 (1.8)	1 (0.5)	1 (0.5)
Cardiac arrest	1 (0.4)	2 (0.7)	1 (0.3)	4 (1.4)	2 (1.1)	2 (1.0)
Stroke	1 (0.4)	3 (1.1)	2 (0.7)	1 (0.4)	1 (0.5)	4 (2.1)

	ECLIPSE-NTG		ECLIPSE-SNP		ECLIPSE-NIC	
	Clevidipine (N=268) n (%)	**Nitroglyrecin (N=278) n (%)**	**Clevidipine (N=296) n (%)**	**Nitroprusside (N=283) n (%)**	**Clevidipine (N=188) n (%)**	**Nicardipine (N=193) n (%)**
Postoperative haemorrhage	1 (0.4)	3 (1.1)	3 (1.0)	3 (1.1)	0 (0)	3 (1.6)

†Only the SAE with a frequency of ≥0.5% in the combined clevidipine groups are presented

There was no difference noted in terms of the occurrence of atrial fibrillation (serious or non-serious) between the clevidipine group and the nitroglyrecin group (33.6% versus 32.0%), or the nitroprusside group (36.1% versus 32.2%) or the nicardipine group (35.6% versus 35.2%).

No difference was observed between clevidipine and its comparators in terms of changes to laboratory test results, especially regarding triglyceride levels.

8.2.2 PSUR data

CLEVIPREX is only marketed in the USA and has been since August 2008 in the indication for "the reduction of blood pressure when oral treatment is not feasible or desirable." The applicant has provided the last PSUR that covers the period from 24 May 2012 to 23 November 2012.
Since August 2008, the number of patients treated with CLEVIPREX is estimated to be approximately 70,000. The applicant's pharmacovigilance database has entries for 138 events (56 serious and 82 non-serious) reported up to the freezing of the database for the last PSUR. Over the period considered in the most recent PSUR, 16 initial reports (5 serious and 11 non-serious) concerning 30 adverse events were received. During this period, analysis of safety data did not highlight any new information regarding previously identified adverse events that could have an impact on the risk benefit ratio for CLEVIPREX, such as those found in the current Summary of Product Characteristics for the product in the USA.

8.2.3 SPC data

The following adverse effects were commonly observed in the perioperative population: atrial fibrillation, sinus tachycardia and hypotension. These events may be related to treatment with this medicinal product, however also to surgical procedures performed. In clinical studies, a reduction in oxygen saturation (reported as hypoxia) was observed in a total of 2.5% of patients receiving clevidipine, compared to 1.5 % receiving nitroglyrecin , 5.1 % sodium nitroprusside and 5.7% nicardipine.

In all phase III clinical studies carried out with heart surgery patients, the incidence of atrial fibrillation for patients treated with CLEVIPREX, compared with those receiving either a comparator or placebo, was 32.8%, 32.9% and 12.0% respectively; this incidence was judged as being treatment-related in 3.9%, 2.5% and 0.0% of cases. The incidence of sinus tachycardia in patients treated with CLEVIPREX in a perioperative setting, compared with those receiving an active comparator or placebo, was 25.5%, 30.5% and 0.0% respectively; this incidence was judged as being treatment-related in 1.3%, 1.2% and 0.0% of cases. The incidence of hypotension in patients treated with CLEVIPREX in a perioperative setting, compared with those receiving an active comparator or placebo, was 15.1%, 14.9% and 1.0%, respectively; this incidence was judged as being treatment-related in 2.5%, 2.5% and 0.0% of cases.

8.2.4 Risk management plan

This proprietary medicinal product has a Risk Management Plan, in particular including monitoring the following "significant" risks:

- Identified risks: non-desired or drastic hypotension, reflex tachycardia and reduction in oxygen saturation,

- Potential risks: nosocomial infection and hyperlipidaemia (hypertriglyceridaemia and pancreatitis).

08.3 Summary & discussion

Two randomised, placebo-controlled, double blind, parallel group, multi-centre studies (ESCAPE-1 –in preoperative - and ESCAPE-2 –in postoperative - setting), on patients with elevated systolic blood pressure were carried out. The failure rate (defined by an absence in a reduction in blood pressure or an inadequate reduction or an intolerance) in the clevidipine group was below that observed in the placebo group.
In these studies, clevidipine enabled a reduction in systolic BP ≥15% compared with baseline values in a median time of 5 to 6 minutes.

Three randomised, open-label studies, with evaluation of the primary endpoint performed by an independent committee without notifying the treatment groups, were carried out:
- in a perioperative setting versus nitroprusside or nitroglyrecin . Currently, no nitroglyrecin -based proprietary medicinal product available in France is indicated in the reduction of blood pressure during the perioperative period.
- in a postoperative setting versus nicardipine.

It should be noted that in the three studies, the primary endpoint was not single but had several criteria (incidence of death from any cause, myocardial infarction, stroke and renal dysfunction), the dosage of the comparators was left to the discretion of the investigators and calculation of the number of patients required was not carried out.

The only difference observed, in favour of clevidipine, was a higher incidence of death from any cause in the nitroprusside group than in the clevidipine group (4.7% versus 1.7%, p=0.04).

Clevidipine was more effective than nitroprusside for maintaining blood pressure within the predefined range during the perioperative period (secondary endpoint). There was no difference highlighted between clevidipine and nicardipine in maintaining blood pressure during the postoperative period.

The incidence of reflex tachycardia was similar between clevidipine and its comparators with 1.4% in the clevidipine and nitroprusside groups, less than 1% in the clevidipine group and no patients in the nicardipine group.

The most commonly observed adverse events with clevidipine during the placebo-controlled studies were: fever, atrial fibrillation, nausea and insomnia. Clevidipine did not lead to a clinically relevant increase in heart rate compared with placebo.
There was no difference highlighted in the safety profile between clevidipine and its nitroprusside or nicardipine comparators, especially in terms of the occurrence of atrial fibrillation.

08.4 Study programmes

An open-label study is currently being carried out within the context of a paediatric investigation plan, validated by the European Health Authorities. This study is evaluating the safety and efficacy of CLEVIPREX in 80 children (neonates, including those who are premature, up to adolescents) undergoing a surgical procedure requiring anaesthesia lasting for more than one hour and for whom the use of intravenous antihypertensive agents is scheduled. The end of this study is planned for February 2016.

09 THERAPEUTIC USE

Due to the mechanisms of the onset of acute perioperative hypertension and how quickly it occurs, treatment differs to that of chronic hypertension. Once the identifiable and reversible factors that increase blood pressure are corrected, such as pain, anxiety, hypothermia, blood volume and hypoxia, the therapeutic management of acute hypertension is based on the use of injectable vasodilating antihypertensive agents, with the aim of reducing systemic vasoconstriction.

In 2002, AFSSAPS guidelines stated that, depending on the circumstances and the treatment aims, short-acting products (nitroprusside and nitroglyrecin) or those with a longer duration of action (nicardipine or urapidil) should be used.[7] Injectable esmolol or labetalol are used if tachycardia is observed.

In the Netherlands, guidelines state:[8]
- within the context of coronary artery bypass graft surgery, nicardipine is to be used in preference over sodium nitroprusside or nitroglyrecin due to the more favourable effect in maintaining ventricular ejection volume and myocardial perfusion. Nicardipine and urapidil conserve myocardial function in a similar way.

- within the context of intracranial surgery, nicardipine and labetalol have a similar efficacy in the lowering of blood pressure without increasing intracranial pressure. Nitroprusside and urapidil are less appropriate in this type of surgery as they increase intracranial pressure.

Clevidipine is a first-line treatment alternative for the rapid reduction of blood pressure in a perioperative setting

[7] AFSSAPS. Poussées hypertensives de l'adulte: élévation tensionnelle sans souffrance viscérale immédiate et urgences hypertensives. May 2002.
[8] Van den Born BJ, Beutler JJ, Gaillard CA, de Gooijer A, van den Meiracker AH, Kroon AA. Dutch guideline for the management of hypertensive crisis - 2010 revision. Neth J Med 2011; 69: 248-55.

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

◗ Acute perioperative arterial hypertension is a common complication, particularly within the context of cardiovascular, intracranial or cancer surgery. Perioperative hypertension is associated with high postoperative morbidity and mortality and is considered as a therapeutic emergency.

◗ This medicinal product is a curative therapy for perioperative hypertension when rapid reduction in blood pressure is indicated.

◗ The efficacy/adverse effects ratio for this medicinal product is high**.**

◗ There are treatment alternatives.

◗ This medicinal product is a first-line therapy.

◗ Public health benefit:
Given that there are alternative treatments available and the absence of an additional impact on the population for public health priorities (reduction in mortality or morbidity, improvement in quality of life, changes to the organisation of healthcare etc.), it is not expected that CLEVIPREX will benefit public health.

Consequently, the Committee considers that the actual benefit of CLEVIPREX is substantial in the rapid reduction of blood pressure in the perioperative setting.

010.2 Improvement in actual benefit (IAB)

Two randomised, open-label (with independent evaluation) studies that compared clevidipine with sodium nitroprusside in a perioperative setting and with nicardipine in a postoperative setting, did not highlight any difference for the primary endpoints that included the incidence of myocardial infarction, stroke and renal dysfunction. The only difference observed, in favour of clevidipine, was a more significant incidence of death from any cause in the nitroprusside group than in the clevidipine group (4.7% versus 1.7%, p=0.04). However, the use of nitroprusside was not found to be an independent factor associated with the increase in mortality in the multivariate analysis. In maintaining blood pressure within a predefined range (which was only a secondary endpoint), clevidipine was more effective than nitroprusside, but there was no difference highlighted versus nicardipine.
Consequently, CLEVIPREX does not provide an improvement in actual benefit (IAB V, non-existent) compared with the two clinically relevant comparators, sodium nitroprusside and nicardipine, in the rapid reduction of blood pressure in a perioperative setting.

010.3 Target population

The target population of CLEVIPREX is represented by the population requiring rapid reduction of blood pressure in a perioperative setting.

Hypotheses regarding the frequency of the use of injectable antihypertensive agents for different types of surgery were established, based on data from the literature[9, 10, 11, 12] and a qualitative study of 20 interviews with French anaesthetists practising in university and non-university hospitals, involved in all types of surgery, carried out by The Medicines Company between August and September 2012, by taking the conservative hypothesis of 1 to 2.5% for "other" types of surgery (percentage estimated in the literature: 4 to 10%).

The main types of surgery during which an injectable antihypertensive agent is used, mentioned by the French anaesthetists, are vascular surgery (carotid artery surgery, endarteriectomy), surgery to the abdominal aorta (and other types of vascular surgery including surgery to the arteries of the lower limbs), heart surgery (coronary artery bypass graft, surgery to the thoracic aorta, valve surgery including replacement valves), neurosurgery (all types of intracranial surgery, including surgery for aneurysm) and general surgery (specifically, pheochromocytoma surgery).

The number of procedures undertaken annually in France per type of surgery was taken from the PMSI database (2011 data). The estimated rate of injectable antihypertensive agent use was applied to the number of procedures (Table 11).

Table 11: Estimation of the target population for CLEVIPREX

Type of surgery	Procedure	Lower hypothesis	Upper hypothesis	Number of procedures in France - 2011	Lower hypothesis	Upper hypothesis
Vascular surgery (except vascular radiology treatment)	Carotid artery surgery (Thrombo-endarteriectomies)	80%	100%	17,294	13,835	17,294
	Surgery to abdominal aorta (clamping of the aorta / replacement of the aorta)	80%	100%	7,994	6,395	7,994
	Other vascular surgery (carotid artery surgery apart from "Thrombo-endarteriectomy")	30%	50%	2,239	672	1,120
	Creation of an arteriovenous vascular access	80%	100%	14,132	11,306	14,132
Heart surgery	Coronary bypass	80%	100%	18,821	15,057	18,821

[9] Goldberg ME, Weaver FA. Strategies for managing perioperative hypertension. Crit Care Clin 2007; 23 Suppl 1: 7-21.
[10] Wax DB, Porter SB, Lin HM, Hossain S, Reich DL. Association of preanesthesia hypertension with adverse outcomes. J Cardiothorac Vasc Anesth 2010; 24: 927-30.
[11] Fontes ML, Varon J. Perioperative hypertensive crisis: newer concepts. Int Anesthesiol Clin 2012 Spring; 50: 40-58.
[12] Varon J, Marik PE. Perioperative hypertension management. Vasc Health Risk Manag 2008; 4: 615-27.

Type of surgery	Procedure	Lower hypothesis	Upper hypothesis	Number of procedures in France - 2011	Lower hypothesis	Upper hypothesis
	Surgery to thoracic aorta (replacement of all or part of the aorta)	80%	100%	2,364	1,891	2,364
	Other heart surgery (Valve replacements / reconstruction of aortic ring)	15%	30%	18,649	2,797	5,595
Neurosurgery	Intracranial neurosurgery (including aneurysm)	20%	40%	14,896	2,979	5,958
General surgery	Pheochromocytoma (rare tumour)	100%	100%	600	600	600
Other surgery with hypertensive patients		1.0%	2.5%	5,517,000	55,170	137,925
TOTAL number of procedures requiring an injectable antihypertensive agent in a perioperative setting					**110,702**	**211,803**

Estimation/conclusion
Based on this data, the target population of CLEVIPREX is estimated to be between 111,000 and 212,000 patients.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends inclusion on the list of medicines approved for hospital use in the indication "*rapid reduction of blood pressure in a perioperative setting*" and at the dosages in the Marketing Authorisation.

◗ Packaging

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