The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

19 January 2011

MEXILETINE AP-HP 200 mg, capsule
B/50 (CIP code: 559 549-8)

Applicant: Etablissement Pharmaceutique de l’AP-HP (Assistance Publique - Hôpitaux de Paris), AGEPS.

Mexiletine hydrochloride
ATC code: M09AX

List I
Medicine for hospital prescription, requiring special monitoring during treatment. Registered on the French "rétrocession" [dispensing of drugs to outpatients by hospital pharmacies] list.

Date of initial Marketing Authorisation: 19/06/1979 (national procedure)

Date of extension of indication “Symptomatic treatment of myotonic syndromes”: 28/06/2010

This extension of the marketing authorisation also confirmed abrogation of the historical indication “ventricular tachycardias”.

Date of latest revision of Marketing Authorisation: 12/10/2010
- drug name changed from MEXITIL 200 mg, capsule to MEXILETINE AP-HP 200 mg, capsule,
- distributor changed from Boehringer Ingelheim France to Etablissement Pharmaceutique de l’AP-HP (Assistance Publique - Hôpitaux de Paris).
- marketing authorisation holder changed from Boehringer Ingelheim France to Assistance Publique - Hôpitaux de Paris (AP-HP)

Reason for request: Inclusion on the list of medicines approved for hospital use in the new indication: “Symptomatic treatment of myotonic syndromes”.

Medical, Economic and Public Health Assessment Division
1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Mexiletine hydrochloride

1.2. Indication
“Symptomatic treatment of myotonic syndromes (myotonic dystrophies and non-dystrophic myotonias or channelopathies).”

1.3. Dosage
Treatment should be started at low dosages and ECGs should be performed (see section 4.4 of the SPC).
Treatment must be started at a dose of 200 mg daily (one capsule a day). The daily dosage can be increased up to 600 mg daily if the clinical symptoms require this. Consequently, maintenance treatment is one to three capsules a day taken at regular intervals throughout the day, adjusted according to the patient's symptoms and clinical response. The daily dosage should not exceed three capsules without enhanced cardiac monitoring (see section 4.3 of the SPC). Capsules should be taken with a glass of water, and the patient should not be lying down when taking them. Patients with digestive intolerance are advised to take the capsules with a meal.

Use in children: In view of the lack of information regarding safety and efficacy in this patient population, this drug is not recommended for use in children.

Use in patients with hepatic insufficiency: The available data are insufficient to allow any dosage adjustment rules to be established for this population because of the lack of reliable data on systemic exposure according to the degree of hepatic insufficiency (see section 4.4 of the SPC). Mexiletine must be used with caution in patients with slight or moderate hepatic insufficiency. Mexiletine is not recommended for use in patients with severe hepatic insufficiency in the absence of data (see sections 4.2 and 4.4 of the SPC).

Use in patients with renal insufficiency: No dosage adjustment seems to be necessary for these patients. Mexiletine is not recommended for use in patients with severe renal insufficiency in the absence of data (see sections 4.2 and 4.4 of the SPC).

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)
M : Musculo-skeletal system
M09 : Other drugs for disorders of the musculo-skeletal system
M09A : Other drugs for disorders of the musculo-skeletal system
M09AX : Other drugs for disorders of the musculo-skeletal system

2.2. Medicines in the same pharmaco-therapeutic category
Not applicable

2.3. Medicines with a similar therapeutic aim
Other sodium channel blockers that can be used to treat myotonic syndromes (off-label use):
carbamazepine (TEGRETOL), phenytoin (DIHYDAN)
Acetazolamide (DIAMOX) indicated in the “Treatment of ocular hypertension”.
Other anti-arrhythmics (off-label use): disopyramide, tocainide, etc.
3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The extension of indication of mexiletine in the symptomatic treatment of myotonic syndromes was validated by the marketing authorisation on the basis of data obtained from a review of the literature.

The pharmaceutical company quoted 20 bibliographical references in support of its application to the Transparency Committee:

Four comparative clinical studies versus placebo and/or active comparator: Kratz 1986\(^1\) and Martens 2005\(^2\) (abstracts which will not be discussed in this opinion), Kwiecinski 1992\(^3\) and Logigian 2010\(^4\).

Three cohort studies: Rossi 1985\(^5\), Meola 1997\(^6\) and Weber 2006\(^7\).

Rossi’s study was an electrophysiological assessment of five patients with congenital myotonia. It will therefore not be discussed in detail in this opinion.

Meola’s study examined the clinical characteristics of myotonia and the efficacy of treatment with mexiletine 200 mg twice daily in 25 patients with type 2 myotonic dystrophy. As this study did not quantify the effect of mexiletine (the only information available is an evaluatement of response to treatment by the prescribing doctors), it will not be discussed in this opinion.

The primary aim of Weber’s study was to ascertain whether the magnetic resonance of sodium could be used to visualise the accumulation of intracellular sodium and the effects of specific treatments for myotonias. It will therefore not be discussed in this opinion.

Three clinical pharmacology studies: These studies were an assessment of functional measurements (Hammaren 2005\(^8\)), or investigated the use of mexiletine in conditions other than myotonia (Kuwabara 2004\(^9\) and Lucetti 2000\(^10\)). They will therefore not be discussed in detail in this opinion.

Nine case studies, each on one or two patients. In view of their methodology, they will not be discussed in this opinion.

A Cochrane review\(^11\) of treatments for myotonia.

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3.1.1. Comparative studies

**Kwiecinski’s study (1992)**

This single-blind study compared the efficacy of mexiletine (MXT), phenytoin (DPH), disopyramide (DPM), tocainide (TCD) and a placebo in 30 adult patients (ages ranging from 18 to 55, average age 31.8) with moderate to severe myotonia: 9 myotonic dystrophies, 9 dominant congenital myotonias (Thomsen’s disease) and 12 recessive myotonias. Comparisons were made with a control group monitored for four weeks.

Treatment efficacy was evaluated according to four criteria:
- time to open the eyelids after maximum contraction
- time to open the hand after maximum contraction
- stair test: time taken to climb 10 steps
- EMG relaxation time.

Each test was repeated three times, with an interval of at least 10 minutes between each attempt.

Results: see table 1

<table>
<thead>
<tr>
<th></th>
<th>Time to open the eyes</th>
<th>Time to open the hand</th>
<th>Time taken to climb 10 steps: stair test</th>
<th>EMG relaxation time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5.3 +/- 3.2 (12)</td>
<td>7.5 +/- 4.9 (30)</td>
<td>16.4 +/- 7.9 (20)</td>
<td>14.1 +/- 7.3 (30)</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.2 +/- 2.9 (12)</td>
<td>7.6 +/- 4.0 (30)</td>
<td>16.8 +/- 6.7 (20)</td>
<td>14.9 +/- 7.2 (30)</td>
</tr>
<tr>
<td>DPM</td>
<td>3.4 +/- 2.0 (8)</td>
<td>4.5 +/- 1.8 (10)</td>
<td>11.8 +/- 3.2 (8)</td>
<td>10.5 +/- 3.9 (10)</td>
</tr>
<tr>
<td>DPH</td>
<td>2.4 +/- 1.7 (11)</td>
<td>3.1 +/- 2.0 (30)</td>
<td>8.9 +/- 3.2 (20)</td>
<td>8.2 +/- 4.6 (29)</td>
</tr>
<tr>
<td><strong>MXT</strong></td>
<td><strong>0.7 +/- 0.9 (8)</strong></td>
<td><strong>1.8 +/- 1.3 (22)</strong></td>
<td><strong>6.3 +/- 2.3 (16)</strong></td>
<td><strong>4.6 +/- 3.3 (22)</strong></td>
</tr>
<tr>
<td>TCD</td>
<td>0.9 +/- 0.7 (8)</td>
<td>1.1 +/- 0.8 (15)</td>
<td>6.0 +/- 1.6 (12)</td>
<td>3.1 +/- 1.8 (15)</td>
</tr>
</tbody>
</table>

The authors concluded that mexiletine and tocainide were the more effective anti-myotonic agents than their comparators (phenytoin, disopyramide, placebo).

The results of this study must be interpreted with caution in view of its methodology (small number of patients taking part, heterogeneity of the patient population, short follow-up time, lack of statistical test).

**Logigian’s study (2010)**

Aim: To evaluate the efficacy and tolerance of mexiletine in terms of reducing myotonic symptoms in patients with dystrophic myotonia (DM1).

Method: Two randomised, double-blind, placebo-controlled studies were conducted on 30 patients with DM1.

The first study compared mexiletine 150 mg three times daily to a placebo, and the second compared mexiletine 200 mg three times daily to a placebo.

These two studies were carried out over two consecutive periods of seven weeks’ treatment (mexiletine/placebo or placebo/mexiletine) separated by a wash-out period of four to eight weeks.

Ten of the 30 patients took part in both studies (eight-week wash-out period between the two studies).
Inclusion criteria: adult patients aged 18 to 80 with DM1 confirmed by clinical and genetic testing, able to walk at least 15 paces alone and having sufficient finger flexion to allow them to grasp a handle.

Primary efficacy endpoint: average time to relax the fingers (defined by a reduction decline in force from 90 to 5%, from 90 to 10% and from 50 to 5%) after deliberate maximum contraction lasting three seconds.

Results: see tables 2 and 3

Table 2: time to relax the fingers (seconds), mexiletine 150 mg three times daily, n=20

<table>
<thead>
<tr>
<th></th>
<th>MEXILETINE 150 mg, three times daily</th>
<th>Placebo</th>
<th>Difference versus placebo [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>On inclusion (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- force 90% to 5%</td>
<td>2.15 (1.28)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- force 90% to 10%</td>
<td>1.61 (1.01)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- force 50% to 5%</td>
<td>1.76 (1.13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 7 weeks of treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- force 90% to 5%</td>
<td>1.32</td>
<td>2.55</td>
<td>-1.23 [-1.81; -0.64]</td>
<td>0.0004</td>
</tr>
<tr>
<td>- force 90% to 10%</td>
<td>0.92</td>
<td>1.76</td>
<td>-0.84 [-1.35; -0.33]</td>
<td>0.003</td>
</tr>
<tr>
<td>- force 50% to 5%</td>
<td>0.98</td>
<td>2.18</td>
<td>-1.19 [-1.79; -0.60]</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

Table 3: time to relax the fingers (seconds), mexiletine 200 mg three times daily, n=20

<table>
<thead>
<tr>
<th></th>
<th>MEXILETINE 200 mg, three times daily</th>
<th>Placebo</th>
<th>Difference versus placebo [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>On inclusion (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- force 90% to 5%</td>
<td>2.80 (1.40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- force 90% to 10%</td>
<td>1.95 (1.09)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- force 50% to 5%</td>
<td>2.39 (1.36)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 7 weeks of treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- force 90% to 5%</td>
<td>1.27</td>
<td>2.63</td>
<td>-1.36 [-2.09; -0.63]</td>
<td>0.001</td>
</tr>
<tr>
<td>- force 90% to 10%</td>
<td>0.98</td>
<td>1.98</td>
<td>-1.00 [-1.63; -0.37]</td>
<td>0.004</td>
</tr>
<tr>
<td>- force 50% to 5%</td>
<td>0.92</td>
<td>2.19</td>
<td>-1.27 [-1.96; -0.57]</td>
<td>0.001</td>
</tr>
</tbody>
</table>

After seven weeks of treatment, the average time to relax the fingers was significantly shorter with mexiletine compared with placebo:
- mexiletine 150 mg, 3 times daily versus placebo:
  - Reduction in force from 90 to 5%: difference -1.23 seconds [-1.81; -0.64], reduction 48%, p=0.0004.
  - Reduction in force from 90 to 10%: difference -0.84 seconds [-1.35; -0.33], reduction 48%, p=0.003.
  - Reduction in force from 50 to 5%: difference -1.19 seconds [-1.79; -0.60], reduction 55%, p=0.0006.
- mexiletine 200 mg, 3 times daily versus placebo:
  - Reduction in force from 90 to 5%: difference -1.36 seconds [-2.09; -0.63], reduction 52%, p=0.001.
  - Reduction in force from 90 to 10%: difference 1.00 seconds [-1.63; -0.37], reduction 51%, p=0.004.
  - Reduction in force from 50 to 5%: difference -1.27 seconds [-1.96; -0.57], reduction 58%, p=0.001.
3.1.2. Cochrane review: Trip 2006

The purpose of this review was to evaluate the efficacy and tolerance of treatments for patients with myotonia.

The studies selected were randomised investigations comparing the study drug with placebo, active treatment or no drug treatment.

This review selected ten studies (n=133, 103 patients with type 1 dystrophic myotonia and 30 patients with congenital myotonia) examining twelve different drugs: procainamide, mexiletine, phenytoin, clomipramine, imipramine, benzodiazepines, calcium antagonists, taurine and prednisone.

Assessment criterias varied according to the study. The methodological quality of the studies is poor: few randomised studies, small cohorts (9 to 30 patients), only per-protocol results available. It was not possible to perform a meta-analysis in view of these methodological shortcomings.

The authors concluded that the possibility of these drugs having beneficial effects in treating myotonias could not be ruled out; their use in treating patients with severe myotonia appears appropriate, but their efficacy and tolerance in treating myotonia cannot be determined because of the lack of high-quality data and randomised studies.

Afssaps has asked AGEPS to conduct an efficacy study of mexiletine in cases on non-dystrophic myotonia. Patient recruitment has not yet started.

3.2. Adverse effects

According to the SPC, the commonest adverse events (> 1%) are:
- Nervous system disorders: somnolence, dizziness, tremor, nystagmus, paresthesia;
- Slight problems: blurred vision;
- Heart conditions: palpitations, bradycardia. Like all drugs with anti-arrhythmic and pro-arrhythmic effects, mexiletine can aggravate existing dysrhythmias or trigger new dysrhythmias;
- Gastrointestinal disorders: dyspepsia, nausea, vomiting, gastric pain;
- Skin conditions: skin rashes.

The anti-arrhythmic and pro-arrhythmic effects are particularly marked in patients with type 1 or 2 myotonic dystrophy, who suffer from frequent cardiac disorders.

In the PSUR covering the period from 3 October 2005 to 3 October 2008 submitted by the pharmaceutical company, eight deaths from cardiac causes were observed in patients being treated with MEXILETINE used as an anti-arrhythmic drug (initial indication).

3.3. Warnings and precautions for use

Pro-arrhythmic effects:
According to the SPC, "Mexiletine can trigger arrhythmia or aggravate an existing arrhythmia, whether or not it has been diagnosed".

A cardiological examination and ECG are recommended before initiating treatment, and during treatment, ECGs should be performed at intervals appropriate to each patient.

In view of the pro-arrhythmogenic effect of class I anti-arrhythmics, especially at the ventricular level, patients undergoing this treatment for myotonic syndrome must have a detailed cardiac examination before the start of treatment, and another examination soon after the start of treatment (for example, within 48 hours) in order to evaluate cardiac tolerance. These examinations should be repeated to monitor the patient’s condition as treatment continues. The onset of cardiac dysrhythmia must prompt the practitioner to reevaluate the benefits of continuing treatment with mexiletine as a matter of urgency.

Type 1 and 2 myotonic dystrophies are associated with an increased risk of rhythm and conduction complications. The risk-benefit ratio must be discussed on a case-by-case basis, taking account of the beneficial effect on myotonia and the risk of rhythm complications.
### 3.4. Conclusions

Several studies have been performed to evaluate the efficacy of mexiletine in patients with myotonic syndrome (three comparative studies and one Cochrane review). These syndromes consist of non-dystrophic or congenital myotonias without any cardiac damage and type 1 or 2 myotonic dystrophies where cardiac damage frequently occurs.

A single-blind study (Kwiecinski, 1992) conducted on 30 adult patients with moderate to severe myotonia found that the anti-myotonic efficacy after four weeks of treatment seemed to be greater in the group treated with mexiletine 200 mg/day than in the groups receiving placebo or “other treatments” (phenytoin, disopyramide, etc.). The results of this study must be interpreted with caution in view of its methodology (single-blind, small number of patients taking part, heterogeneity of the patient population, short follow-up time, lack of statistical test).

The Cochrane review (Trip, 2006) which examined ten studies on patients with myotonic syndrome concluded that the possibility of drugs used in myotonia (including mexiletine) proving beneficial could not be ruled out, that their use in cases of severe myotonia seemed appropriate but that the efficacy and tolerance of these treatments for myotonia could not be determined in view of the absence of good-quality data and randomised studies.

Two randomised, double-blind studies (Logigian, 2010) were conducted on 30 patients with type 1 myotonic dystrophy. They found that the average time to relax the fingers after seven weeks’ treatment was reduced more markedly with mexiletine than with placebo: by 48 to 55% with mexiletine 150 mg three times daily and by 51 to 58% with mexiletine 200 mg three times daily.

According to the SPC, the most common adverse events (> 1%) are: somnolence, dizziness, tremor, nystagmus, paresthesia, blurred vision, dyspepsia, nausea, vomiting, gastric pain, skin rashes, palpitations and bradycardia.

Like all class I anti-arrhythmics, mexiletine has a pro-arrhythmogenic effect and can aggravate existing rhythm disorders or trigger new rhythm disorders. In view of this pro-arrhythmogenic effect, patients undergoing treatment for myotonic syndrome must have a detailed cardiac examination before the start of treatment, and another examination soon after the start of treatment (for example, within 48 hours) in order to evaluate cardiac tolerance. These examinations should be repeated to monitor the patient’s condition as treatment continues. The onset of cardiac dysrhythmia must prompt the practitioner to reevaluate the benefits of continuing treatment with mexiletine as a matter of urgency, and to discontinue it if appropriate.

Types 1 and 2 myotonic dystrophy, in which cardiac damage frequently occurs, are associated with an increased risk of rhythm or cardiac conduction disorders. The risk-benefit ratio of mexiletine must be discussed on a case-by-case basis, taking account of the beneficial effect on myotonia and the risk of rhythm complications. Except in special cases, mexiletine is not recommended for patients with documented ventricular rhythm disorders or impaired ventricular function (LVF < 45%) because of its pro-arrhythmic effect.

### 4. TRANSPARENCY COMMITTEE CONCLUSIONS

#### 4.1. Actual benefit

Myotonias are conditions characterised by problems with muscular decontraction, which form a disabling handicap that can impair quality of life. They can be multi-system conditions and can, if the heart or lungs are affected, be life-threatening (types 1 and 2 myotonic dystrophy).
This proprietary medicinal product is part of treatment addressing the symptoms.

This medicinal product is a first-line therapy.

In the light of the clinical data available, the efficacy/adverse effects ratio of this proprietary medicinal product in the extension of indication is:
- moderate for patients with non-dystrophic or congenital myotonia with no cardiac damage,
- minor for patients with type 1 or 2 myotonic dystrophy for which cardiac damage occurs frequently, because of the pro-arrhythmogenic effect of mexiletine.

**Public health benefit:**
Myotonias are serious, disabling and potentially life-threatening conditions, but are a minor public health burden because they are so rare (orphan disease). Improving the management of patients with orphan diseases, including myotonias, is a public health need that is an established priority (Law of 9 August 2004 concerning public-health policy, Rare Diseases Plan).

In view of the limited clinical data available and the absence of quality of life data, it is not possible to quantify the anticipated impact of the proprietary medicinal product MEXILETINE AP-HP in terms of morbidity, mortality and quality of life.

It is not certain that MEXILETINE AP-HP could contribute to meeting the established public health need.

Consequently, and in view of the small size of the population concerned, no public health benefit is anticipated from placing the proprietary medicinal product MEXILETINE AP-HP on the market in this indication.

Alternative drug therapies are used on an off-label basis.

The actual benefit of MEXILETINE AP-HP in its extension of indication is:
- moderate for patients with non-dystrophic or congenital myotonia with no cardiac damage,
- minor for patients with type 1 or 2 myotonic dystrophy for which cardiac damage occurs frequently.

### 4.2. Improvement in actual benefit (IAB)

In view of the clinical data available, MEXILETINE AP-HP provides:
- a moderate improvement in actual benefit (IAB III) in the management strategy of patients with non-dystrophic or congenital myotonia without cardiac damage,
- a minor improvement in actual benefit (IAB IV) in the management strategy of patients with type 1 or 2 myotonic dystrophy for which cardiac damage occurs frequently.

### 4.3. Therapeutic use

Myotonic syndromes are conditions characterised by difficulty in relaxing the muscles, associated with hyperexcitability of the muscle fibre membrane. The condition is divided into two groups according to whether or not an underlying dystrophic process is present: non-dystrophic myotonia and dystrophic myotonia (types 1 and 2 myotonic dystrophia).

**Non-dystrophic myotonias:**
Non-dystrophic myotonias are conditions in which the myotonia is generalised and causes severe discomfort, but where the heart is not damaged. They are caused by mutations of genes coding for the muscles’ chlorine or sodium ion channels. They can be separated into three major groups: congenital myotonias, congenital paramyotonias and sodium channel myotonias. Treatment is selected according to the discomfort that the patient experiences. Substances which block the sodium channels, such as mexiletine, carbamazepine or diphenylhydantoin, are used.

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12 www.orpha.net
Congenital myotonias, such as Thomsen's disease and Becker's disease, are forms of myotonia characterised by improvement in response to effort (warm-up phenomenon). They are rarely painful and mainly affect the muscles in the lower limbs. They vary in severity, ranging from isolated, episodic symptoms to almost permanent contraction.

Congenital paramyotonia, or Von Eulenburg's disease, is characterised by persistent myotonia triggered by exercise and aggravated by cold, and is accompanied by muscle weakness. It mainly affects the face and hands, but some patients can also suffer paralytic attacks following attacks of stiffness. These forms of paramyotonia hardly progress at all and are not life-threatening, but can cause severe handicap.

Sodium channel myotonias include various non-dystrophic myotonic syndromes. The three major syndromes are fluctuating myotonia (myotonia fluctuans), permanent myotonia (myotonia permanens) and acetazolamide-responsive myotonia. They are characterised by the onset of myotonia in childhood or adolescence, the severity of which varies according to the syndrome which is present. In the permanent form, the pharyngeal and respiratory muscles can be affected and attacks of dyspnea can occur. Some patients describe a clear warm-up phenomenon while others report a worsening of their myotonia on exertion (paradoxical myotonia). However, they never suffer from paralytic attacks and their sensitivity to cold is inconsistent. Myotonia is worsened by the ingestion of potassium, which is why these conditions have also been called "potassium-aggravated myotonias".

Patients with non-dystrophic myotonia rarely suffer cardiac damage.

Myotonic dystrophies:
These dystrophies are characterised by myotonias which are usually less severe but are frequently associated with cardiac damage, especially dysrhythmia.

Type 1 myotonic dystrophy (DM1) or Steinert's disease is the most common form of muscular myotonic dystrophy in adults. It is characterised by multi-system damage; various degrees of severity of muscular deficit, dysrhythmia and/or cardiac conduction disorder, cataract, endocrine damage, sleep disorders and hair loss can occur. Patients should ideally have an annual multidisciplinary check-up. The disease normally progresses slowly, but rapid worsening can sometimes be observed. Life expectancy is impaired as patients have higher mortality as a result of pulmonary and cardiac complications.

Type 2 myotonic dystrophy (DM2) is a multi-system condition characterised by a range of problems including but not limited to proximal motor deficit (scapular and pelvic girdles) associated with frequent myalgia, tremor, cardiac damage with rhythm and conduction disorders and possible cardiomyopathy, posterior capsular cataract, endocrine disorders with hyperhidrosis, testicular atrophy, insulin resistance and diabetes. Multidisciplinary management and monitoring, particularly for cardiac problems, is recommended for patients with DM2. The prognosis is related to the presence and extent of cardiac damage.

Role of MEXILETINE AP-HP
MEXILETINE AP-HP is a first-line symptomatic treatment for non-dystrophic myotonias and myotonic dystrophies.

Practitioners considering whether to prescribe MEXILETINE AP-HP for patients with type 1 or 2 myotonic dystrophy must evaluate the risks and benefits for each patient and must refer patients to a consultant cardiologist in a reference or competence centre for neuromuscular diseases.

All additional examinations (Holter ECG, exertion test where appropriate, endovascular electrophysiological investigation, etc.) which may be useful to ensure that MEXILETINE AP-HP is not having a pro-arrhythmic effect can be conducted at the request of the cardiologist. Mexiletine is not recommended for patients with documented ventricular rhythm disorders or impaired ventricular function (LVF < 45%) because of its pro-arrhythmic effect.
4.4. Target population
The target population for MEXILETINE AP-HP is comprised of patients with myotonic syndrome (myotonic dystrophy and non-dystrophic myotonia or channelopathy). It can be estimated from the following data (Source: ORPHANET).

Non-dystrophic myotonias:
- Congenital Thomsen and Becker myotonia: 1 to 10 in 100,000 individuals.
- Congenital Eulenburg paramyotonia: 0.6 in 100,000 individuals.
- Potassium-aggravated myotonia: very few cases have so far been identified.
- Hyperkalaemic primitive periodic paralysis: fewer than 1 in 100,000 individuals.

Myotonic dystrophies:
- Type 1 (Steinert’s disease): prevalence of 1 in 20,000 individuals,
- Type 2: prevalence of 1 in 100,000 individuals.

Insufficient epidemiological data is available to allow any estimate to be formed of the proportion of asymptomatic patients and patients with cardiac damage who cannot for this reason be treated with MEXILETINE. It is therefore impossible to clearly establish the target population of MEXILETINE.

As a guide, around 550 patients in France are currently being treated with MEXILETINE.

The data available and the opinions of experts indicate that the maximum target population for MEXILETINE is 700 patients.

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

Prescription conditions:
MEXILETINE AP-HP is a drug for hospital prescription, requiring particular monitoring during treatment. The Transparency Committee believes that patients due to receive this treatment must be seen by a cardiologist specialising in neuromuscular conditions.