HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

4 February 2009

MIMPARA 30 mg, film-coated tablets
Pack of 14 (CIP: 365 154-8)
Pack of 28 (CIP: 365 155-4)
Pack of 30 (CIP: 365 157-7)
Pack of 84 (CIP: 365 156-0)

MIMPARA 60 mg, film-coated tablets
Pack of 14 (CIP: 365 158-3)
Pack of 28 (CIP: 365 160-8)
Pack of 30 (CIP: 365 162-0)
Pack of 84 (CIP: 365 161-4)

MIMPARA 90 mg, film-coated tablets
Pack of 14 (CIP: 365 163-7)
Pack of 28 (CIP: 365 164-3)
Pack of 30 (CIP: 365 167-2)
Pack of 84 (CIP: 365 166-6)

Applicant: AMGEN S.A.S.

Cinacalcet hydrochloride

ATC Code (2008): H05BX01

List I

Date of MA and its variations: 22 October 2004 (centralised procedure)
19 June 2008 (extension of indication - centralised procedure)

Reason for request: inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospital in the extension of indication “Reduction of hypercalcaemia in patients with primary hyperparathyroidism for whom parathyroidectomy would be indicated on the basis of serum calcium levels (as defined by relevant treatment guidelines), but in whom parathyroidectomy is not clinically appropriate or is contraindicated”.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Cinacalcet (hydrochloride)

1.2. Indications

“Treatment of secondary hyperparathyroidism (HPT) in patients with end-stage renal disease (ESRD) on maintenance dialysis therapy.
Mimpara may be used as part of a therapeutic regimen including phosphate binders and/or Vitamin D sterols, as appropriate.

Reduction of hypercalcaemia in patients with:

- parathyroid cancer
- ***primary hyperparathyroidism for whom parathyroidectomy would be indicated on the basis of serum calcium levels (as defined by relevant treatment guidelines), but in whom parathyroidectomy is not clinically appropriate or is contraindicated****”.*

1.3. Dosage

"Oral route, as clinical studies have shown that the bioavailability of cinacalcet is increased when taken with food, it is recommended that Mimpara be taken with food or shortly after a meal (see section 5.2). Tablets should be taken in one piece and not cut into pieces.

Hepatic impairment:
No change in starting dose is necessary. Mimpara should be used with caution in patients suffering from moderatetosevere hepatic impairment, and treatment should be closely monitored during the dose titration phase as well as during the continuation of the treatment.

Secondary hyperparathyroidism

Adults and elderly (> 65 years)
The recommended starting dose for adults is 30 mg once a day. Mimpara should be titrated every 2 to 4 weeks untilt a maximum daily dose of 180 mg is reached , in order to achieve targeted parathyroid hormone (PTH) levels, comprised between 150 and 300 pg/ml (15.9-31.8 pmol/l), in dialysis patients in the intact PTH (iPTH) assay. PTH levels should be assessed at least 12 hours after dosing with Mimpara. Reference should be made to current treatment guidelines.
PTH should be measured 1 to 4 weeks after initiation or dose adjustment of Mimpara. PTH should be monitored approximately every 1-3 months during the maintenance period. Either the intact PTH (iPTH) or bio-intact PTH (biPTH) may be used to measure PTH levels; treatment with Mimpara does not alter the relationship between iPTH and biPTH.
Information concerning the pharmacokinetics/pharmacodynamics (PK/PD) of cinacalcet are grouped together in section 5.1.
During dose titration, serum calcium levels should be monitored frequently, and within 1 week of initiation or dose adjustment of Mimpara. Once the maintenance dose has been established, serum calcium should be measured approximately monthly. If serum calcium levels decrease below the normal range, appropriate corrective measures should be (see section 4.4). Concomitant treatments by phosphate binders and/or vitamin D analogs should be adjusted according to requirements.

Children and adolescents
Safety and efficacy have not been established in patients under the age of 18 years.

Parathyroid carcinoma and primary hyperparathyroidism

Adults and elderly (> 65 years)
The recommended starting dose of Mimpara for adults is 30 mg twice per day. The dose of Mimpara should be titrated every 2 to 4 weeks through sequential doses of 30 mg twice daily, 60 mg twice daily, 90 mg twice daily, and 90 mg three or four times daily as needed to reduce serum calcium concentration to or below the upper limit of normal. The maximum dose used in clinical trials was 90 mg four times daily.
Serum calcium should be measured during the first week following the initiation or following each dose adjustment of Mimpara. Once maintenance dose levels have been established, serum calcium should be measured every 2 to 3 months. After titration to the maximum dose of Mimpara, serum calcium should be periodically monitored; if clinically relevant reductions in serum calcium are not maintained, discontinuation of Mimpara therapy should be considered.

Children and adolescents
Safety and efficacy have not been established in patients under the age of 18 years."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

H	: systemic hormones, excluding sex hormones and insulins
H05	: medicinal products ensuring calcium homeostasis
H05B	: anti-parathyroid agents
HB05BX	: other anti-parathyroid agents
HB05BX01	: cinacalcet

2.2. Medicines in the same therapeutic category

Not applicable

2.3. Medicines with a similar therapeutic aim

Biphosphonates and calcitonin are indicated in the treatment of hypercalcaemia associated with malignancy.

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The company submitted 5 phase II studies:

3.1.1 A total of 150 patients with mild to moderate primary hyperparathyroidism were included in 4 of these studies (980125, 990160, 990120, 20000159).

These studies were submitted with the initial MA application of MIMPARA.
EMEA performed a grouped analysis of the data obtained during the examination of the extension of indication. In the MIMPARA EPAR[1], enrolled patients were divided into 3 sub-groups for this analysis:

- Patients with persistent or recurrent primary hyperparathyroidism after parathyroidectomy (failure of parathyroidectomy)
- Patients with at least one of the criteria for surgical intervention in parathyroidectomy[2] but who were not operated (46% of included patients)
- Other patients

It was also specified in the EPAR[1] that data concerning the contraindications to surgery were only collected in 1 study out of 4.
The main data of these studies are given in *tables 1* (dose-titration studies) *and 2* (fixed-dose studies).

Table 1: dose-titration studies

Study/Method	Main inclusion criteria	Sample size	Duration/Dose	Endpoints	Results
980125 Randomised, double-blind, placebo-controlled	Primary HPT: - iPTH ≥ 45 pg/ml - Serum calcium levels > 10.3 mg/dl and ≤ 12.5 mg/dl	1st phase: Cinacalcet : n=32 Placebo: n=8 2nd phase: Cinacalcet : n=16 Placebo: n=6	1st phase: - 6 weeks - 50, 75, 100 mg/day in 1 dose 2nd phase: - 2 weeks - 60, 80, 100 mg/day in 2 doses	% of patients with serum calcium levels ≤ 10.3 mg/ml on last day of treatment	1st phase: 50 mg/day : 83% 75 mg/day: 58% 100 mg/day: 50% Placebo: 75% 2nd phase: 50 mg/day: 100% 75 mg/day: 100% 100 mg/day: 80% Placebo: 67%
990120 Randomised, double-blind, placebo-controlled	See study 980125	Cinacalcet : n=40 Placebo: n=38	Titration: - 12 weeks - from 60 to 80 or 100 mg/day in 2 doses Maintenance: - 12 weeks - 60, 80 or 100 mg/day in 2 doses Follow-up during treatment: 28 weeks	1) % of patients with mean serum calcium ≤ 10.3 mg/ml 2) % of patients with mean reduction in serum calcium ≥ 0.5 mg/dl in maintenance phase	1) Cinacalcet 88% Placebo: 5% 2) Cinacalcet : 90% Placebo: 13%

HPT: hyperparathyroidism ; iPTH : intact parathyroid hormone;

1 www.emea.europa.eu

2 Indications for surgical treatment of asymptomatic primary hyperparathyroidism according to the NIH: 1) serum calcium concentration > 1 mg/dl above the accepted normal reference range; 2) 24-hour urinary calcium excretion > 400 mg ; 3) creatinine clearance reduced by more than 30% for age ; 4) reduction in bone density : T-score < 2.5 SD in lumbar spine, hip or distal radius; 5) patients under 50 years of age ; 6) medical surveillance impossible. In: Bilezikian J.P., Potts J.T., Fuleihan G.E.H.*et al* . Summary statement from a workshop on Asymptomatic Primary Hyperparathyroidism: A Perspective for the 21st century. J.C.E.M, 2002. 87(12)5353-5361.

Table 2: Fixed-dose studies

Study/Method	Main inclusion criteria	Sample size	Duration/Dose	Endpoints	Results
990160 Randomised, double-blind, placebo-controlled	Primary HPT: - iPTH > 45 pg/ml, - Serum calcium levels≥ 11.0 mg/dl	Cinacalcet : n=6 Placebo: n=4	- 4 weeks - 130 mg/day in 2 doses	Reduction in mean calcium levels from D7 to D28	Cinacalcet : 16.2% Placebo: 5.8%
20000159 Open-label, uncontrolled	Patients who completed study 990120 (active and placebo groups)	n= 45	Titration † : - 12 weeks - 60 to 100 or 120 mg/day in 2 doses Maintenance - 4.5 years - 60, 100 or 120 mg/day in 2 doses	% of patients with serum calcium levels < 10.3 mg/ml throughout study	80%

HPT: hyperparathyroidism ; iPTH : intact parathyroid hormone; †: Dose titration criteria not available

The grouped analysis made by EMEA on the data of the 4 studies showed a reduction in the serum calcium levels in each of the 3 patient subgroups defined above. This reduction was maintained for the duration of treatment, with however large individual variations and standard deviations[3].
This grouped analysis did not show a significant difference for plasma iPTH levels between the patients treated by Mimpara and patients who received the placebo[3].

3.1.2 Pivotal study (20000204), performed in patients with more severe hyperparathyroidism: Parathyroid carcinoma or intractable primary HPT.

Interim results of this study were submitted with the initial MA application for Mimpara (29 patients were included including 21 with parathyroid carcinoma).

Method:

- Inclusion criteria:
  - Parathyroid carcinoma
  - Intractable primary HPT: Failure of or contraindication to parathyroidectomy.
- Study design: Open-label, uncontrolled study comprising a dose-titration phase from 2 to 16 weeks with weekly visits and a maintenance phase with visits every 8 weeks.
- Primary efficacy endpoint: proportion of subjects with a reduction in serum calcium levels ≥ 1mg/dl at the end of the dose-titration phase.
- Secondary endpoints:
  - Proportion of subjects with serum calcium levels within normal limits: ≤10.3 mg/dl at the end of the titration phase
  - Absolute levels, change relative to baseline levels, percent change relative to baseline levels for serum calcium N-telopeptide and bone alkaline phosphatase and intact plasma PTH intact at the end of the titration phase
  - Safety
- Statistical analysis
  - The required sample size was calculated using the result of study 990120 in which 79% of treated patients had a reduction in serum calcium levels ≥ 1mg/dl at the end of the titration period. The calculated sample size was 50 patients: this is required to give limits of the 95% confidence interval of the percentage patients with a reduction in serum calcium levels ≥ 1mg/dl at the end of the titration period of 67 and 90% .

3 EPAR of Mimpara - www.emea.europa.eu

- All enrolled subjects were included in the statistical analysis (descriptive analysis).

- Treatment: The starting dose was 60 mg in two doses. It was then titrated according to serum calcium levels and tolerability up to a maximum dosage of 360 mg/day in 4 separated doses. Dose escalation was stopped when the serum calcium levels were ≤10 mg/dl, when the authorised maximum daily dosage was reached or in the case of adverse effects.

Results:

- Forty-six patients were included. Their main characteristics are given in *table 3*:

Table 3: Baseline characteristics

	Parathyroid carcinoma (n=29)	Primary HPT (n=17)
Women - n Men - n	15 14	8 9
Average age (years) ± standard deviation	51 ± 14.4	65.7 ± 9
Mean baseline serum calcium concentrations ± standard deviation (mg/dl)	14.1 ± 2.31	12.7 ± 0.75
Mean baseline iPTH ± standard deviation (pg/ml)	697.3 ± 497	243.4 ± 105
Median baseline iPTH levels (pg/ml)	491	266.5
Mean baseline bone alkaline phosphatase levels ± standard deviation (ng/ml)	72.6 ± 110.8	60.4 ± 110.7
Mean baseline N-telopeptide levels ± standard deviation (nM)	110.3 ± 143.9	78.8 ± 158.6

- Exposure:
  - For patients with primary HPT, the mean duration of treatment was 347 ± 283 days (standard deviation) (32 to 1105 days) and for thyroid cancer patients it was 335 ± 306 days (standard deviation) (1 to 1051 days).
  - The median dose was 270 mg per day in 3 doses at the end of the titration phase and at the end of the study for thyroid cancer patients; it was 140 mg per day in 2 doses at the end of titration phase and 120 mg per day in 2 doses at the end of the study for primary HPT patients.
- Primary efficacy endpoint:

  At the end of the dose-titration phase, 33 enrolled patients out of 46, including 15/17 with primary HPT and 18/29 with thyroid cancer had a reduction in serum calcium ≥ 1mg/dl.
- Secondary endpoints:

  Their results are given in *table 4.*

Table 4: Secondary endpoints

Values at the end of the titration period	Parathyroid carcinoma (n=29)	Primary HPT (n=17)
Patients with mean serum calcium ≤ 10.3 mg/d (n; %)	18 ; 17%	9 ; 53%
Mean serum calcium ± SE* (range) (mg/dl)	12.4 ± 0.5 (8.9 -17.4)	10.4 ± 0.3 (8.5 – 12.7)
Mean reduction in serum calcium ± SE* (mg/dl)	1.7 ± 0.63	2.3 ± 0.32
Mean reduction in serum calcium ± SE* (%)	9.7 ± 4.73	17.9 ± 2.3
Mean iPTH levels ± SE* (pg/ml)	593 ± 67.7	396 ± 158.2
Median iPTH levels (pg/ml)	686	173
Mean change in iPTH levels ± SE* (%)	- 6.1 ± 7.27	- 2.6 ± 13.65
Mean bone alkaline phosphatase levels ± SE*(ng/ml)	114.2 ± 28.9	82.2 ± 37
Mean N-telopeptide levels ± SE* (nM)	142.9 ± 37.8	168.1 ± 118.9

* : standard deviation of the mean

3.2. Safety

3.2.1 Studies including patients with mild to moderate primary hyperparathyroidism (980125, 990160, 990120, 20000159).

The main results are given in *tables 5 and 6*:

Table 5: dose-titration studies

Study/Method	Sample size	Duration/Dose	Endpoints	Results
980125 Randomised, double-blind, placebo-controlled Dose-titration	1st phase: Cinacalcet : n=32 Placebo: n=8 2nd phase: Cinacalcet : n=16 Placebo: n=6	1st phase: - 6 weeks - 50, 75, 100 mg/day in 1 dose 2nd phase: - 2 weeks - 60, 80, 100 mg/day in 2 doses	- % patients with 1 AE; 1 SAE; discontinued trial for intolerance; - Main adverse effects*	1st phase: - Cinacalcet : AE: 66% SAE: 0 Withdrawals : 75 mg/33%, 100 mg/50% - Placebo: AE: 13% 2nd phase: - Cinacalcet : AE: 25% SAE: 0 - Placebo: AE: 33% - Dizziness, myalgia, nausea, paraesthesia
990120 Randomised, double-blind, placebo-controlled	Cinacalcet : n=40 Placebo: n=38	Titration: - 12 weeks - from 60 to 80 or 100 mg/day in 2 doses† Maintenance: - 12 weeks - 60. 80 or 100 mg/day in 2 doses Follow-up during treatment: 28 weeks	- % patients with 1 AE; 1 SeAE, 1 SAE; trial discontinuations for intolerance; - Main adverse effects*	Cinacalcet AE: 55% SeAE: 15% SAE: 0 Withdrawals : 20% - Placebo: AE: 32% SeAE: 5% SAE: 0 Withdrawals : 16% - nausea, myalgia, paraesthesia

AE: adverse effect (treatment-related); SeAE: severe adverse effect; SAE: serious adverse event;* : Related to cinacalcet treatment and occurring in more than 10% of patients during the 2nd phase; †: Related to cinacalcet treatment and occurring in more than 10% of patients;

Table 6: Fixed-dose studies

Study/Method	Sample size	Duration/Dose	Endpoint	Results
990160 Randomised, double-blind, placebo-controlled	Cinacalcet : n=6 Placebo: n=4	- 4 weeks - 130 mg/day in 2 doses	- % patients with 1 AE; 1 SeAE, 1 SAE; trial discontinuations for intolerance; - Main adverse effects	- cinacalcet: AE: 50% SeAE: 17% SAE: 0 Withdrawals: 0% - Placebo: AE: 0% - nausea, abdominal pain, paraesthesia
20000159 Open-label, uncontrolled extension of study 990120	n= 45	Titration†: - 12 weeks - 60 to 100 or 120 mg/day in 2 doses Maintenance - 4.5 years - 60, 100 or 120 mg/day in 2 doses	- % patients with 1 AE; 1 SAE; trial discontinuations for intolerance; - Main adverse effects	AE: 29% SAE: 0 Withdrawals : 4% arthralgia, myalgia and diarrhoea

AE: adverse effect (treatment-related); SeAE: severe adverse effect; SAE: serious adverse event.

3.2.2 Pivotal study (20000204), in patients with more severe hyperparathyroidism: parathyroid carcinoma or intractable primary HPT.

Eighty-five percent of patients (39/46) presented at least one adverse effect (considered to be treatment-related); 9% of patients (4/46) presented a serious adverse effect and 2% (1/46) a life-threatening adverse effect. The most frequent adverse effects were nausea and vomiting.

Twenty percent of patients (9/46) discontinued treatment because of an adverse event. The most common serious adverse events were: hypercalcaemia, fracture and dehydration.

Eight patients died during the study; no death was considered to be related to treatment.

3.2.3 Conclusion of the EPAR for all studies:

The analysis of studies carried out in the EPAR concluded that the safety profile of Cinacalcet was similar in each of the 5 studies in patients presenting primary hyperparathyroidism. In the double-blind studies, nausea, dizziness, fatigue, diarrhoea and paraesthesia were more frequent in the Cinacalcet groups than in the placebo groups. The most common adverse event was nausea.

3.3. Conclusion

The company submitted 5 phase II studies.

Four of these studies were dose-titration and/or safety studies. Patients with mild to moderate primary hyperparathyroidism were included. In these studies:139 were given different doses of Mimpara and 56 received placebo. EMEA conducted a grouped analysis of data from these studies during the examination of the extension of indication. This analysis showed an immediate reduction in serum calcium levels in treated patients which was maintained for the duration of the treatment, though there were large individual variations and standard deviations[4] .

In a non-comparative open-label study, 46 patients with more severe hyperparathyroidism including 29 with parathyroid carcinoma and 17 with intractable primary HPT (failure or contraindication to parathyroidectomy) were included. At the end of dose titration period, 15 of the 17 patients with intractable primary HPT had a reduction in serum calcium levels ≥ 1mg/dl; 9/17 had serum calcium levels ≤10.3 mg/d.

In the double-blind studies, nausea, dizziness, fatigue, diarrhoea and paraesthesia were more frequent in the Cinacalcet groups than in the placebo groups. The most common adverse event was nausea.

4 EPAR of Mimpara - www.emea.europa.eu

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

- Primary hyperparathyroidism may cause serious complications such as calcium lithiasis, fibrocystic osteitis, chondrocalcinosis, osteoporosis, asthenia, depression and gastrointestinal disorders[5].
- These proprietary medicines are intended for curative and symptomatic treatment.
- The efficacy/safety ratio is high.
- Public health benefit
  Although, secondary hypercalcaemia due to primary hyperparathyroidism is a serious illness, it represents a low public health burden because of the small number of patients affected .
  Taking into account existing treatments, the management of this clinical condition does not constitute a public health need. However, MIMPARA provides a useful clinical option when parathyroidectomy is contraindicated or not clinically appropriate.
  In these situations, MIMPARA may decrease morbidity and mortality and improve quality of life. However, it is impossible to evaluate the expected benefit.
  Consequently, in the current state of knowledge, MIMPARA is not expected to benefit public health in this indication.
- Mimpara is intended for second-line treatment in patients, who have either a contraindication to or have failed surgery.
- There are alternative treatments.
- The actual benefit of this proprietary product is substantial.

4.2. Improvement in actual benefit

Mimpara, provides a moderate improvement in actual benefit (IAB III), in the treatment of hypercalcaemia in patients with primary hyperparathyroidism who have either a contraindication to or have failed parathyroidectomy.

4.3. Therapeutic use

4.3.1 Indications for surgery in HPT

SFE Guidelines [6] :
Surgery is the first-line treatment for patients presenting asymptomatic primary hyperparathyroidism, provided that it is not dangerous because of other diseases or a precarious general health status and after discussion with the patient.
If first-line surgery is impossible or not accepted as a choice, medical surveillance may be recommended, *provided that patients do not meet any of the following major criteria:*

- Age < 50 years,
- Clinical symptoms or tissue lesions caused by hypercalcaemia (urinary lithiasis, renal stones, bone signs, chondrocalcinosis etc.)
- Serum calcium concentrations ≥ 110 mg/ml or 2.75 mmol/l with normal proteins (ionized calcium is not used as the assay is more difficult to perform)
- Urinary calcium excretion > 400 mg/24h or 10 mmol/24

5 Cazalda-Nocaudie M, Chanson P, Conte-Devoux B *et al.* Management of primary asymptomatic hyperparathyroidism, SFE expert consensus -2005-WW.endocrino.net
6 Cazalda-Nocaudie M, Chanson P, Conte-Devoux B et al. Management of primary asymptomatic hyperparathyroidism, SFE expert consensus -2005-WW.endocrino.net

- A reduction in the filtration rate estimated with the MDRD formula (preferably) (or Cockroft and Gault formula with its limits in elderly patients) below 60 ml/min/1.73m2 establishes the diagnosis of chronic renal disease
- Bone density (DXA) with a T-score ≤ -2.5 SD at any site. To be evaluated at 2 sites, the femoral neck is the 1st reference site (as measurement in the lumbar spine becomes less reliable with age).
  No consensus for the densitometric diagnosis of osteoporosis (based on the T-score) in males.

NIH Guidelines[7] :
Surgery for primary hyperparathyroidism is recommended in the following cases:

- Age < 50 years,
- Adequate medical surveillance is impossible
- Serum calcium concentration > 1mg/dl above the accepted normal reference range
- Urinary calcium excretion > 400 mg/24h
- Reduction of 30% in renal function
- Development of complications of primary hyperparathyroidism including renal stones, osteoporosis (T-score < 2.5 SD for lumbar spine, hips or wrist) or severe neuropsychological dysfunction.

4.3.2 Therapeutic use

Mimpara is used for second-line treatment of hypercalcaemia in patients presenting with primary hyperparathyroidism who have either a contraindication to or have failed parathyroidectomy.

4.4. Target Population

The prevalence of primary hyperparathyroidism in Europe is about 2/1000[8]. The number of patients aged 18 years or more with primary hyperparathyroidism may therefore be estimated at approximately 99,000 persons.
Symptomatic forms account for 20% of these cases[9] i.e. 19,800 persons.
The failure rate of surgical treatment after a first operation is between 3 and 5% and the proportion of patients who fail a second operation is about 0.5 to 1% (expert opinion). The number of patients who may benefit from surgical treatment but who cannot be operated is not known; however contraindications to surgical treatment are rare because of the development of mini-invasive surgical techniques and the opportunities offered by local anaesthesia (expert opinion). The proportion of inoperable patients may be estimated between 1% and 2 %.
The target population of MIMPARA in this indication is therefore about 250 to 560 patients.

7 Bilezikian J.P., Potts J.T., Fuleihan G.E.H.et al . Summary statement from a workshop on Asymptomatic Primary Hyperparathyroidism: A Perspective for the 21st century.
8 Dalemo S, Hjerpe P, Boström Bengtsson k. Diagnosis of patients with raised serum calcium level in primary care, Sweden. Scandinavian journal of primary Health Care, 2006;24:160-165
9 Cazalda-Nocaudie M, Chanson P, Conte-Devoux B et al. Management of primary asymptomatic hyperparathyroidism, SFE expert consensus -2005-WW.endocrino.net

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use in the hospital and various public services in the new indication and at the dosage of the MA.

4.5.1 Packaging: Appropriate for the prescription conditions

4.5.2 Reimbursement rate: 65%