

PRODUCT MONOGRAPH

Pr. TRIMEBUTINE

Trimebutine Maleate Tablets

100 mg and 200 mg

Lower gastrointestinal tract motility regulator

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^{Pr}TRIMEBUTINE

Trimebutine Maleate Tablets

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THERAPEUTIC CLASSIFICATION

Lower gastrointestinal tract motility regulator

CLINICAL PHARMACOLOGY

TRIMEBUTINE (trimebutine maleate) is a noncompetitive spasmolytic agent. It possesses moderate opiate receptor affinity and has marked anti-serotonin activity especially on 'M' receptors. It induces regulation of spontaneous activity and increases synchronization between electrophysiological spikes and contractions in isolated guinea pig strips of colon and ileum. However, it does not alter normal motility, but regulates abnormal intestinal activity.

Comparative Bioavailability

A comparative bioavailability study was performed using healthy human volunteers. The rate and extent of absorption of trimebutine was measured and compared following oral administration of 1 x 200 mg of Trimebutine or Modulon tablets. The results from measured data are summarized as follows:

Summary Table of the Comparative Bioavailability Data Trimebutine Maleate (Dose: 1 x 200 mg) From Measured Data			
Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**
	Trimebutine	Modulon®†	
AUC _T (ng•hr/mL)	55.7 69.6 (61)	61.4 75.1 (59)	90.8
AUC _I (ng•hr/mL)	59.1 73.8 (63)	65.3 79.9 (60)	91.8
C _{max} (ng/mL)	36.7 49.3 (77)	42.1 52.2 (64)	87.1
T _{max} (hr)*	0.80 (47.4)	0.70 (28)	-
t _{1/2} (hr)*	2.77 (63)	3.11 (66)	-
* Arithmetic means (CV%).			
** Based on the least squares estimate.			
† Modulon® is manufactured by Axcan Pharma, and was purchased in Canada.			

INDICATIONS AND CLINICAL USE

TRIMEBUTINE (trimebutine maleate) is indicated:

- for the treatment and relief of symptoms associated with the irritable bowel syndrome (spastic colon), and
- in postoperative paralytic ileus in order to accelerate the resumption of the intestinal transit following abdominal surgery.

CONTRAINDICATIONS

TRIMEBUTINE (trimebutine maleate) is contraindicated in patients with known hypersensitivity to trimebutine maleate or any of the excipients.

No other contraindications have been identified at this time.

WARNINGS

Although teratological studies have not shown any drug related adverse effects on the course and outcome of pregnancy in laboratory animals by both oral and parenteral routes, the use of TRIMEBUTINE (trimebutine maleate) in pregnant women is not recommended.

Children: Not recommended for use in children under 12 years of age.

PRECAUTIONS

Drug Interactions: Animal studies have shown that trimebutine maleate increases the duration of d-tubocurarine-induced curarization. No other drug interactions have been observed during clinical trials or otherwise reported.

ADVERSE REACTIONS

In clinical studies, adverse effects of mild to moderate nature occurred in 7% of the patients treated with trimebutine maleate. No single side effect occurred in more than 1.8% of the patients and some of these might have been related to the patient's condition rather than the medication. The commonly reported adverse effects are as follows: a) Gastrointestinal: Dry mouth, foul taste, diarrhea, dyspepsia, epigastric pain, nausea and constipation were reported in total of 3.1% of the patient population; b) CNS: Drowsiness, fatigue, dizziness, hot/cold sensations and headaches were reported in 3.3%; c) Allergic reactions: Rash in 0.4% of the patients; and d) Miscellaneous effects: Menstrual problems, painful enlargement of breast, anxiety, urine retention and slight deafness were also infrequently reported.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional poison control centre immediately.

No evidence of overdose has been reported to date. However, if overdose should occur following oral administration of TRIMEBUTINE (trimebutine maleate), gastric lavage is recommended. Treatment should be made according to the symptoms observed.

DOSAGE AND ADMINISTRATION

The adult recommended dose is up to 600 mg daily in divided doses. It may be administered as two 100 mg tablets three times daily before meals or one 200 mg tablet three times daily before meals.

PHARMACEUTICAL INFORMATION

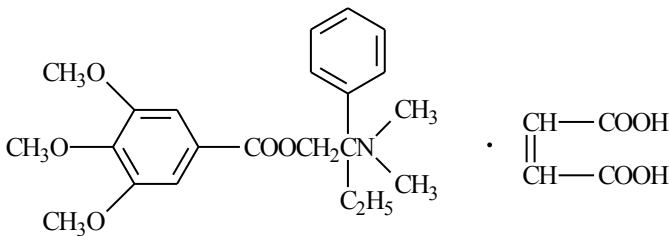
DRUG SUBSTANCE

Proper/Common Name: Trimebutine maleate

Chemical Name: 2-dimethylamino-2-phenyl-butyl-3,4,5-trimethoxybenzoate maleate

Molecular Formula: $C_{22}H_{29}NO_5 \cdot C_4H_4O_4$

Structural Formula:



Molecular Weight: 503.6 g/mol

Description: Trimebutine is a white to off-white powder practically insoluble in water, sparingly soluble in ethanol, ether, n-hexane, methanol and freely soluble in acetone and chloroform.

Melting point: 78°C to 82°C

Trimebutine maleate: The maleate salt of trimebutine ($C_{22}H_{29}NO_5 \cdot C_4H_4O_4$; M.W.: 503.6 g/mol) is a white to off-white powder (M.P. 128°C to 134°C) very slightly soluble in ether and n-hexane, sparingly soluble in water,

soluble in acetone, ethanol and methanol and freely soluble in chloroform.

COMPOSITION

In addition to trimebutine maleate, TRIMEBUTINE 100 mg and 200 mg tablets contain the non-medicinal ingredients magnesium stearate and methylcellulose.

Stability and Storage Recommendations

Store at room temperature (15°C to 30°C).

AVAILABILITY OF DOSAGE FORMS

TRIMEBUTINE 100 mg: each white, round, biconvex tablet, scored and engraved "TMB" over "100" on one side contains 100 mg of trimebutine maleate. Available in bottles of 100, 250 and 500, and in unit dose packages of 100.

TRIMEBUTINE 200 mg: each white, round, biconvex tablet, scored and engraved "TMB" over "200" on one side contains 200 mg of trimebutine maleate. Available bottles of 100, 250 and 500, and in unit dose packages of 100.

PHARMACOLOGY

ANIMAL PHARMACOLOGY

In isolated smooth muscle preparations, trimebutine maleate was shown to be a noncompetitive spasmolytic agent. It was found to be as active as papaverine against acetylcholine, histamine, barium or serotonin on 'D' receptors; however, it was more active against nicotine or serotonin on

'M' receptors. This potent anti-serotonin activity is non-specific and may be, at least partly, attributed to its local anaesthetic activity, as shown in comparative studies with lidocaine. Using membrane preparations of whole rat brain and guinea pig intestine, trimebutine maleate was shown to bind to opiate receptors with moderate affinity.

Electrophysiological studies have shown that trimebutine maleate exerts a strong spasmolytic papaverine-like activity together with an evident, unusual stimulation of spontaneous activity. It induced a marked regularization of spontaneous activity with an increase in the amplitude of contractions. A clear synchronization with the appearance of large regular spikes closely coupled to the single contractions was also noted. However, unlike quinidine-like drugs, the membrane resistance was not concomitantly increased.

The effects of trimebutine maleate on the mechanical and electrical activity of the intestine are not prevented by atropine or hexamethonium, but the spasmolytic activity is counteracted by an increase in calcium concentration.

In vivo, trimebutine maleate did not alter normal intestinal transit time in mice and rats, but regularized abnormal intestinal activity by increasing transit time when abnormally low or by decreasing it when abnormally high, thus returning transit time towards normal values. A similar regularizing effect was noted on Oddi's sphincter in rabbits. It was less active than atropine against the intestinal spasmogenic effect of methacholine, but more active than papaverine against other spasmogens such as barium or prostigmin in mice, rats and rabbits.

The effect of trimebutine maleate administered orally or intravenously was studied in conscious or anaesthetized rabbits, dogs and sheep and the mechanical and/or electrical activity was recorded in some or all of the following segments: stomach, duodenum, jejunum, ileum, and colon. Gastric

activity remained unaltered or was slightly depressed; the depressant effect was much less than that with N-butylscopolamine and atropine and more than with papaverine, while metoclopramide had the opposite effect. The activity of the small intestine was markedly increased, more in the duodenum than in the jejunum and ileum and preferentially in those segments with irregular intestinal activity. This effect was more pronounced with trimebutine maleate than with metoclopramide, while papaverine had a depressant effect. In dog colon, trimebutine maleate has a less pronounced but more sustained effect which consisted of a stimulant action on circular muscles coupled with an inhibitory action on longitudinal muscles. In the rabbit, the experimentally-induced hyperpolarization of the colon was decreased in amplitude or suppressed, while a facilitation effect on synaptic excitatory potentials was noted which might have been related to an action on purinergic neurons. No other noticeable effects were observed on the gastrointestinal tract.

Trimebutine maleate was shown to be a potent local anaesthetic with activity which is greater in magnitude and longer in duration than cocaine, procaine and lidocaine.

On the central nervous system, trimebutine maleate dosed at 2 to 30 mg/kg i.v., 2 to 100 mg/kg i.p. and 2 to 500 mg/kg p.o. in mice, rats and rabbits produced some of the following effects depending upon the species, the dosage and the route of administration: reduced spontaneous activity, hypotonia, slight sedation and impairment of cortical reactivity, increased sleep duration and decreased duration of induced hyperactivity, anticonvulsant activity and amidopyrine-like analgesia. Trimebutine maleate depressed respiration rate and amplitude and produced respiratory arrest at high doses.

In the cardiovascular system of dogs and rabbits, trimebutine maleate produced vasodilation as illustrated by increased coronary and femoral blood flow, and a dose related, but transient fall in systolic and diastolic blood pressure; ECG was not modified.

PHARMACOKINETICS

Metabolic studies in rat, dog and man showed the C¹⁴-trimebutine maleate or its free base is rapidly absorbed after oral administration. Peak plasma concentrations of radioactivity were observed within one hour in man and rat and within 2 to 4 hours in the dog.

Plasma radioactivity in man indicated a kinetic model with central and peripheral compartments and a mean distribution half-life of 0.66 hour. Tissue distribution studies showed high concentration of the radiolabelled drug in the stomach and the intestinal walls of rat and in the major organs of metabolism and excretion in mice. Placental transfer without teratogenic effect was observed in the rat. Protein-binding was less than 5% in vivo (rat plasma) and in vitro (bovine serum albumin).

Urine was the main route of elimination in all species while a small percentage (5 to 12%) of radioactivity was detected in the faeces. The plasma half-life of trimebutine was short, but the elimination half-life of radioactivity was approximately 10 to 12 hours in man and rat. In the rat, an entero-hepatic circulation was also demonstrated.

Extensive metabolism of the parent compound was indicated since less than 2.4% of the urinary radioactivity was found as unchanged drug in all species. The livers of rat and dog appeared to be the major site of hydrolysis of the ester and also capable of a "first pass" metabolism.

The main urinary metabolites in all species were 2-amino (I) or 2-methylamino (II) or 2-dimethylamino-2-phenylbutan-1-ol (III). These three metabolites plus mono-N-desmethyl trimebutine (IV) were also shown in plasma; the major component was III in rat and dog and IV in man. Sulphate and/or glucuronic acid conjugation was also shown to play an important role in metabolism.

CLINICAL PHARMACOLOGY

Clinical data have confirmed the regulating effects of trimebutine maleate on lower gastrointestinal tract. This data is based on intestinal electromyographic recordings or by stool transit time determinations in patients with postoperative paralytic ileus or in patients suffering from irritable bowel syndrome (IBS). In addition, these regulating effects were also confirmed by sigmoid motor activity in patients with hypo- or hypersigmoid activity.

Irritable Bowel Syndrome

Trimebutine maleate has been extensively used in various clinical trials involving subjects with irritable bowel syndrome. A total of 18 studies were conducted on 744 patients to evaluate the effects of trimebutine maleate. Eleven of these 18 studies were double-blind controlled trials (363 patients) in which trimebutine maleate was compared with placebo. In three other controlled trials (130 patients), trimebutine maleate was compared with mebeverine, a papaverine-like drug, and the remaining four trials (251 patients) were of open design.

Among the controlled studies, three were short-term (3-day treatment) involving 197 patients and eight were medium-term (2 to 4 weeks treatment) studies with a total population of 166 patients. The doses used in these trials varied between 400 to 600 mg per day in divided doses with the 100 mg tablet formulation. Most of these studies used a single or double-blind cross-over design in order to reduce the bias of placebo effects.

Assessment of treatment efficacy was carried out by evaluating the severity of each of the symptoms before and during treatment (abdominal pain, constipation, diarrhea, etc). as absent, mild, moderate or severe. Alternatively, the degree of symptom improvement was assessed. In addition, an overall evaluation of patients' preference for any of the study medications was also recorded.

A placebo effect was observed in most of these studies during the initial treatment period, i.e. there was no difference in the symptom improvement between the trimebutine and placebo groups. On the subsequent treatment periods, however, trimebutine appeared to be more efficacious than placebo.

Short-Term Studies: In one of the three short-term cross-over studies (3-day treatment), trimebutine maleate was significantly superior to placebo regardless of whether it was taken as the first or the second treatment. In the other two studies, patients receiving trimebutine maleate as the second treatment improved significantly more than those on placebo.

Medium-Term Studies: Seven of eight studies were double-blind, cross-over whereas one was parallel design. The duration of the treatment varied from two to four weeks and the dosage ranged between 300 to 600 mg daily. The following symptoms were evaluated: abdominal pain, constipation, diarrhea and distention/flatulence. Global evaluation and patients' preference for a specific treatment were recorded at the end of the treatment period.

In three of these studies, the efficacy of trimebutine maleate was superior to placebo; the improvement was statistically significant. Also, analysis of single stool transit time(one study) showed a significant acceleration of transit in patients receiving trimebutine maleate, the median stool transit time being reduced from 52 to 25 hours ($p < 0.05$). Evaluation of data from the global assessment of symptom severity made by the patient and the physician further indicated that severity of symptoms ameliorated in more patients on trimebutine maleate than on placebo. Furthermore, the patients with the most severe initial symptoms demonstrated improvement when given trimebutine maleate.

The results of one study indicated that the effect of trimebutine maleate became evident only after two weeks and persisted for one more week after the therapy was discontinued. In this study, trimebutine maleate gave better improvement than placebo which was significant ($p < 0.01$) with regard to alternating constipation and diarrhea. In other studies, although subjects showed a statistically significant improvement during treatment compared to pre-treatment, there was no significant difference between trimebutine and placebo.

In other controlled trials, trimebutine maleate was compared with mebeverine, a papaverine-like medication. A total of three studies involving 130 patients were conducted. Trimebutine maleate 100 or 200 mg t.i.d. and mebeverine 100 mg t.i.d. or q.i.d. was administered up to four weeks in patients suffering from irritable bowel syndrome. Both drugs provided statistically significant improvement ($p < 0.001$) of the symptoms of irritable bowel syndrome after two and four weeks of treatment without any significant difference between the two groups. However, the improvement obtained with trimebutine maleate during third and fourth week of treatment was significantly superior ($p < 0.001$) to that observed with mebeverine. The tolerance was excellent for both drugs.

In a recently published double-blind, placebo controlled study conducted by Shannon et al, trimebutine maleate (200 mg) was administered orally to 11 normal volunteers and nine patients with constipation-predominant irritable bowel syndrome. The postprandial motor activity was measured manometrically in the sigmoid colon.

Results indicated that, although orally administered, trimebutine maleate had no effect on post prandial sigmoid motor activity in normal subjects. Nonetheless, it attenuated the increase observed in patient with constipation-predominant irritable bowel syndrome.

In another, double-blind, cross-over study conducted by Schang et al, trimebutine maleate 200 mg daily was administered orally for one month to 24 patients suffering from chronic idiopathic constipation. Results indicated that colonic transit time was significantly reduced ($p < 0.05$) with trimebutine maleate in patients with "delayed" transit time (from 105 ± 9 to 60 ± 11 hours) while it did not change with placebo (from 103 ± 17 to 95 ± 10 hours). Electrical activity was not influenced by trimebutine maleate or placebo in constipated patients with "normal" transit time, neither before nor after meals.

Post-Operative Paralytic Ileus

Controlled Studies: Five controlled and 11 open studies were performed to evaluate the clinical effects of trimebutine maleate on postoperative ileus. These studies included 1,123 patients (controlled studies: 340 patients, and open studies: 783 patients).

In the controlled studies, trimebutine maleate was administered at doses of 100 to 400 mg by intravenous or intramuscular routes. Overall results indicated that trimebutine maleate was well tolerated by patients. The time interval to passage of first intestinal gas was shorter in trimebutine maleate treated patients (52 ± 9 hours) as compared to placebo group (73 ± 17

hours). Also, the resumption of intestinal motility was significantly faster (68 ± 11 hours) in comparison with placebo (88 ± 18 hours) ($p < 0.05$). In addition, patients in trimebutine maleate group felt less abdominal discomfort than those in placebo group.

Adverse side effects, such as dizziness, nausea and/or vomiting, diarrhea and dry mouth, were reported by 14 of 340 patients (4.1%). These adverse effects were mild in nature and did not require concomitant medication.

Open Studies: In the 11 open studies, resumption of gases appeared within 48 hours in 66.4% of cases while in 85.4% it appeared within 72 hours. As in the controlled studies, trimebutine maleate helped in improving the postoperative conditions of patients as their abdominal and colonic discomfort, abdominal pain and nausea decreased.

Results indicated that trimebutine maleate had an intense contractile activity on the intestine of the 29 patients treated with the drug compared to 13 patients who did not receive it. Clinically, the study showed that the duration of paralytic ileus was notably shorter in patient treated with trimebutine maleate than in the control group. The passage of the first postoperative gas was reduced by an average of 23% by trimebutine maleate. It was also noted that trimebutine maleate attenuated the symptoms associated with ileus, namely nausea, vomiting, distention and abdominal pain.

TOXICOLOGY

Acute Toxicity

The acute toxicity of trimebutine maleate estimated by various routes of administration gave the following results (LD₅₀ in mg/kg ± S.E.)

	<u>MOUSE</u>	<u>RAT</u>	<u>RABBIT</u>
Oral	>5000	>5000	2500 ± 800
i.p.	500 ± 46	550 ± 55	- *
i.v.	43 ± 3	16 ± 3	- *

* i.p. and i.v. studies in the rabbit were not performed.

Death was produced by respiratory arrest within 1 minute, 15 minutes and 24 hours after i.v., i.p. or oral dosing, respectively.

The acute i.v. toxicity was studied in anaesthetized dogs with the monitoring of cardiovascular and respiratory functions. At dose levels in the range of 1 to 20 mg/kg, dose related reductions in respiratory rate and arterial blood pressure were observed.

Death due to respiratory arrest occurred at 49 mg/kg. Cardiac function persisted for almost three minutes after respiratory arrest; therefore, the death occurred due to the respiratory arrest and not due to effect on the cardiovascular system.

Subacute Toxicity

Trimebutine maleate was injected intravenously for four weeks to rats and beagle dogs at doses of 4, 8 and 16 mg/kg/day or 4, 7 and 12.5 mg/kg/day, respectively.

In rats, no specific organ toxicity was observed. In the high dose group, however, there was a high mortality rate since half of the animals died during the study. Death occurred always within 15 seconds of dosing and the animals exhibited signs of acute CNS involvement. Postmortem examination showed a slight weight increase of spleen and adrenals in males at 16 mg/kg/day. The injection sites were of normal appearance.

In dogs, transient, reversible signs of CNS effects were apparent at 7 and 12.5 mg/kg/day. An overall weight loss was observed in the high dose females while weight gain was decreased in males at 7 and 12.5 mg/kg/day. The injection sites of treated and control animals were comparable.

Chronic Toxicity

Trimebutine maleate was administered orally for 26 weeks to rats and beagle dogs at dose levels of 40, 220 and 1,210 mg/kg/day or 10, 30 and 90 to 250 mg/kg/day, respectively.

In rats, no overt clinical signs nor identifiable specific target organ toxicity were observed. In the high dose groups, a low incidence of mortality occurred. Weight gain decreased at 1,210 mg/kg/day in males and females and in females dosed with 220 mg/kg/day. A moderate elevation of SAP and SGPT appeared at the end of the treatment period in the high dose female group. At 1,210 mg/kg/day, liver and adrenal weights (relative to body weights) were increased, while kidney weights increased in the high dose groups. Histopathological examination did not reveal any abnormalities.

In dogs, adverse clinical signs and weight loss were confined to animals dosed at 250 mg/kg/day. A dose related decreased coagulation time was observed at 90 and 250 mg/kg/day, which was also associated with reduced prothrombin time. At the high dose level, serum albumin decreased

while blood urea nitrogen, blood creatinine and liver, kidney or adrenal weights increased. There were no histopathological abnormalities considered related to treatment.

Teratology

In rats, teratogenicity studies, fertility and general reproductive studies and pre and postnatal studies were undertaken by the oral and i.m. routes at doses of 100-1,000 mg/kg and 12.5-50 mg/kg, respectively. In teratogenicity studies in rabbits, trimebutine maleate was administered orally and subcutaneously at doses of 50-200 mg/kg and 25-100 mg/kg, respectively.

Mutagenicity

No teratogenic abnormalities were found during the course of these studies and trimebutine maleate had no adverse effects on fertility, reproduction, course and outcome of pregnancy and offspring development during lactation.

In vivo, mutagenicity study in mice at dose levels of 3,000-12,000 mg/kg and in vitro mutagenicity and carcinogenicity studies failed to show any evidence of bone marrow toxicity or mutagenic and carcinogenic potential of trimebutine maleate.

REFERENCES

1. Arzac M. Expérimentation clinique du débridat en chirurgie générale. *Hip Inf. Therap.* 1972; 3, 2: 103-106.
2. Bantman C. Conclusions d'une application du débridat en médecine pratique dans les colopathies. *Hop Inf. Therap.* 1972; 3, 4: 213-214.
3. Cinqualbre J, Lampert M, Avalos S, Forster E. Essai clinique d'un nouveau péristaltogène agissant au niveau des synapses digestives. *J. Med. Strasbourg* 1973; 4, 12:973-976.
4. Cope A. Étude clinique comparative de l'association clidinium (br)-chlordiazepoxide et de la trimébutine dans le traitement des colopathies fonctionnelles. *Med. Chir. Dig.* 1981; 10, 8: 713-717.
5. Corazza G R, Vaira D, Milletti S, Vanzini S, Gasbarrini G. Controlled clinical evaluation of pinaverium bromide and trimebutine in functional disorders of the colon. *Acta Therapeutica* 1983; 9:383-389.
6. Dika-N'Sangue, Ekwe, Bell, Lartizien. La trimébutine: médicament dans les suites opératoires de la chirurgie abdomino-pelvienne. *Gas. Med. France* 1974; 81, 3: 276-278.
7. Dornier R. Expérimentation clinique de la trimébutine. *Ann. Med. Nancy* 1972; 11: 1647-1651.
8. Fabre P, Izquierdio Ch, Mayeux Cl, Parneix M. Intérêt postopératoire de la trimébutine en chirurgie abdominale. *Bordeaux Medical* 1973; 2: 203-208.
9. Fielding J F. Double-blind trial of trimebutine in the irritable bowel syndrome. *Ir. Med. J.* 1980; 73, 10:377-379.
10. Francillon J, Philippe MP. Essais en chirurgie abdominale d'une nouvelle molécule, la trimébutine, dans les reprises du transit postopératoire. *Lyon Med.* 1971; 225, 4:363-365. *Gaz Med France* 1971; 5, 30: 39-42.
11. Frexinos J, Fioramonti J, Bueno L. Effect of trimebutine on colonic myoelectrical activity. *Fur. J. Clin. Pharmaco.* 1985; 28: 181-185.
12. Grenier J F, Schang J C, Dauchel J. Étude électromyographique des effets de la trimébutine sur la motricité intestinale au cours de la période postopératoire. *J Med Strasbourg* 1977; 8, 5: 335-338.
13. Guilmin M. Étude du débridat dans les suites de la chirurgie abdominale. *Arch. Med. Ouest* 1973; 5, 4.
14. Isman H, Lupo B, Narache R. Effet débridat (trimébutine) sur la motricité sigmoïdienne et recto-sigmoïdienne chez le sujet normal et chez le colopathe. *Gax. Med. France* 1982; 89, 11: 1272-1276.

15. Lagache G, Dumont, Chevert J, Proye C. Appréciation clinique de l'efficacité de la tolérance de la trimébutine dans les reprises de transit postopératoire en chirurgie abdominale. *Lille Med* 1971; 16, 8, supp. 4: 1209-1210.
16. Le Bras J Y. Contribution à l'étude clinique de l'action de la trimébutine sur le comportement de l'appareil digestif après intervention en chirurgie abdominale majeure. *Ouest Medical* 1973; 26, 3: 317-320.
17. Lee SW. Essai clinique de la ploytubine sur des patients présentant des symptômes du côlon irritable. *Le Nouveau Journal Médical* 1981; 24, 9.
18. Luttecke K. A three-part controlled study of trimebutine in the treatment of irritable colon syndrome. *Curr. Med. Res. Opin.* 1980; 6, 6: 437-443.
19. Luttecke K. A trial of trimebutine in spastic colon. *J. Int. Med. Res.* 1978; 6, 2: 86-88.
20. Malavaud A. Essai de la trimébutine dans la reprise du transit digestif en chirurgie abdominale. *Anesth Analg Rea* 1972; 29, 1: 65-69.
21. Meunier P. Effets de la trimébutine sur la motricité colique dans les colopathies. *Gastroenterol Clin Biol* 1980; 4, Ibis: 261A.
22. Moctezuma U, Gastro B, Leon B, Guerra I. Trimebutine en el tratamiento del colon irritable. *Invest Med Int* 1977; 4, 1: 71-74.
23. Moine D, Picard P. Une nouvelle thérapeutique dans les suites opératoires de la chirurgie abdominale et dans les troubles du transit intestinal. *Gaz Med France* 1971; sup. 30: 43-44.
24. Moshal M G, Herron M. A clinical trial of trimebutine (Mebutin) in spastic colon. *J. Int. Med. Res.* 1979; 7, 3: 31-234.
25. Reboa G, Bertoglio C, Terrizzi A, et al. L'azione della trimebutina sull'attività elettrica e manometrica del colon normale e patologico. *Rivista Di Gastro-Enterologia* 1976; 28, 1: 1-16.
26. Sarna S, Chevy WY, London R E, Dodds WJ, Myers T, Chang TM. Cause-and-effect relationship between motilin and migrating myoelectric complexes. *Am. J. Physiol* 1984; 245: G277-G284.
27. Sasaki D, Kido A, Yoshida Y. Effect of antispasmodic drugs on the colonic motility II: Clinical study in man. *Int J Clin Pharmacol Ther Toxicol* 1984; 22, 7: 338-341.
28. Schang JC, Devroede G, Pilote M. Beneficial effects of trimebutine in patients suffering from irritable bowel disease (IBS) with normal transit or constipation. *Gastroenterology* 1988; 94 (5): 403.
29. Shannon S, Hollingsworth J, Cook JJ, Collins SM. Effects of trimebutine on postprandial colonic motor activity in healthy subjects and patients with irritable bowel syndrome. *Gastrointestinal Motility* 1989; 1(1): 9-14.
30. Stoppa R, Petit J. Résultats de l'utilisation de la trimébutine en chirurgie abdominale. *J Sci Med Lille* 1972; 90, 8: 319-320.

31. Tete R, Grossetete JL. La trimébutine en gastro-entérologie. Cahiers Médicaux Lyonnais 1971; 47, 35: 3971.
32. Toulemonde H. Action de la trimébutine (Débridat) sur la reprise du transit après intervention digestive. Rev Med Toulouse 1972; 8, 4.
33. Toussaint J, Cremer M, Pintens H. Etude en simple aveugle de la trimébutine et de la mébévérine dans le côlon irritable et la dyspepsie. Acta Ther 1981; 7, 3: 261-268.
34. Valori R, Shannon S, Reddy N, Daniel EE, Collins SM. The action of trimebutine maleate on gastrointestinal motility is mediated by opiate receptors in human subjects. Gastroent Clin Biol 1987; 11: 102B-104B.
35. Vergues J. La trimébutine dans le traitement de l'iléus paralytique postopératoire en chirurgie abdominale. J Med Montpellier 1972; 7, 7: 369-372.
36. Product Monograph - Modulon[®] (trimebutine maleate) 200 mg, Aptalis Pharma Canada, Inc. Date of revision: November 2, 2011 Control No.: 150622.