This Summary of Clinical Study Report is provided for patients and healthcare professionals to demonstrate the transparency efforts of the Menarini Group. This document is not intended to replace the advice of a healthcare professional and can't be considered as a recommendation. Patients must always seek medical advice before making any decisions on their treatment. Healthcare Professionals should always refer to the specific labelling information approved for the patient's country or region. Data in this document can not be considered as prescribing advice.

The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

2. SYNOPSIS

Laboratoire MENARINI France		**Reference to part IV**	**For national authority use only**
Name of medicinal product: Ketum® 2.5% gel		**Volume:**	
Name of active substance: ketoprofen		**Pages:**	
Study title	A phase IV, randomised, double-blind, double-dummy, two parallel group study: KETUM® 2.5% gel versus oral diclofenac 50 mg in symptomatic hand osteoarthritis		
Study Centres	94 French General Practitioners - 64 active centres (which included at least one patient)		
Publication			
Study period	2007 – 2008 Date of inclusion of 1st patient: 28 March, 2007 Date of end of study for last patient: 31 May, 2008	Phase IV	
Objective	To compare the symptomatic efficacy and safety of KETUM® 2.5% gel versus oral diclofenac in symptomatic hand osteoarthritis, with the hypotheses of equivalent efficacy and better safety of KETUM® 2.5% gel.		
Methodology	A comparative, multi-centre, phase IV, double-blind, double-dummy, equivalence trial on two parallel groups of patients presenting with symptomatic hand osteoarthritis and treated for 7 days, either with KETUM® 2.5% gel 3 doses 3 times a day, or with oral diclofenac 25 mg x 2, 3 times a day. Consisting of 3 visits: ▪ D1: inclusion visit. ▪ D3 ± 1: intermediate visit. ▪ D7 ± 1: end of study visit.		
Number of patients	*Planned:* 400 included – 326 Per protocol evaluable patients *Included*: 398 patients (Ketum® 2.5% gel: 198; oral diclofenac: 200) *Per protocol analysis:* 334 patients (Ketum® 2.5% gel: 164; oral diclofenac: 170)		
Screening criteria	*Inclusion criteria*: ▪ Men or women, 45 to 75 years of age (limits included), ambulatory patients. ▪ With osteoarthritis of the digits and/or osteoarthritis of the thumb, – In a painful episode for more than 2 days and less than 7 days with the following: ◆ Overall spontaneous pain of the hands during the last 24 hours greater than 40 mm on a Visual Analogue Scale (VAS) ranging from 0 to 100 mm [1-2]. ◆ Dreiser's functional index score for arthropathies of the hand [3] greater than or equal to 5. – Meeting criteria of the American College of Rheumatology[4]*:* Pain, tenderness or stiffness of the hands and at least 3 of the 4 following criteria: ◆ Bone thickening of at least 2 of 10 selected joints (2nd and 3rd DIP, 2nd and 3rd PIP and the trapezo-metacarpal joints of both hands). ◆ Thickening of at least 2 distal interphalangeal joints (DIP). ◆ Swelling of at least 3 metacarpophalangeal joints (MCP). ◆ Deformity of at least 1 of the 10 selected joints. ▪ Patient who is a beneficiary of the social security system ▪ Patient who agreed to provide his consent to participate in the study in writing after having been informed of the study procedures. ▪ Able to understand instructions on the study and to fill out a self-evaluation diary. ▪ Whose adherence with specificities of the study protocol is predictable.		

Laboratoire MENARINI France	**Reference to part IV**	**For national authority use only**
Name of medicinal product: Ketum® 2.5% gel	**Volume:**	
Name of active substance: ketoprofen	**Pages:**	

Screening criteria (continued)

Exclusion criteria:

- Patient with hand osteoarthritis secondary to:
  - direct trauma to the hand (dislocation, fracture, contusion).
  - a known metabolic arthropathy: chondrocalcinosis (defined as the presence of a calcium border on the triangular carpal ligament), gout, haemochromatosis.
- Patient with a painful disorder of the hand or the upper limb, which can interfere with evaluation of osteoarthritis of the digits, such as:
  - A scar or Dupuytren's disease, resulting in functional disability,
  - Carpal tunnel syndrome,
  - Tendinitis of the hand, elbow or shoulder,
  - Recent trauma less than 2 months ago,
  - Painful sequelae of fracture, dislocation or surgery,
  - Algodystrophy,
  - Cervico-brachial neuralgia or another neurological tunnel syndrome (ulnar, thoracic outlet syndrome, etc) or a neurological disorder of the upper limb (A.L.S., M.S., poliomyelitis),
  - Paget's disease or another osteopathy
  - An inflammatory (psoriatic rheumatism, ankylosing spondylitis, rheumatoid arthritis, scleroderma, etc), infectious or tumour disease,
- Patient presenting with a disorder contraindicating the use of any one of the study treatments:
  - A wound or skin lesion involving the area to be treated,
  - Known hypersensitivity to ketoprofen, to diclofenac, to the excipients in the products or to NSAIDs,
  - Allergic reactions (urticaria, acute rhinitis, asthma) during treatment with aspirin (or any other agent containing a cyclooxygenase inhibitor) or with fenofibrate or during application of a sunscreen product or a fragrance.
  - Previous history of gastro-duodenal ulcer or progressive ulcer,
  - Previous history of GI bleeding,
  - Progressive sigmoiditis or colitis (ulcerative colitis, Crohn's disease),
  - Asthma or a previous history of asthma,
  - Haemophilia, coagulation disorders,
  - Uncontrolled severe heart failure,
  - Uncontrolled arterial hypertension or history of severe cardiovascular disease, in particular coronary artery disease,
  - Severe renal or hepato-cellular failure,
  - A progressive or uncontrolled serious pulmonary, haematological or neoplastic disease,
  - Congenital galactosemia, glucose malabsorption syndrome, lactase deficiency.
- Patient who cannot avoid exposure to the sun or to UVA radiation during the treatment period and during the 2 weeks after the end of the study.
- Previous or concomitant unauthorised treatment:
  - Application of any topical agent on the hands (including cosmetics) during the 8 hours prior to inclusion and throughout the duration of the study.

Laboratoire MENARINI France	**Reference to part IV**	**For national authority use only**
Name of medicinal product: Ketum® 2.5% gel	**Volume:**	
Name of active substance: ketoprofen	**Pages:**	

Screening criteria (continued)	*Exclusion criteria* (continued) ▪ Previous or concomitant unauthorised treatment (continued) − Treatment with an analgesic agent: ◆ WHO level I (paracetamol, nefopam) during the 12 hours prior to inclusion and throughout the duration of the study, ◆ WHO level II (weak opioids) or WHO level III (strong opioids) during the 48 hours prior to inclusion and throughout the duration of the study, ◆ Systemic NSAIDs, even at analgesic dosage (ibuprofen), during the 3 days (15 days for oxicams) prior to inclusion and throughout the duration of the study, ◆ Systemic salicylates, even aspirin at anti-aggregant dosage, during the 3 days prior to inclusion and throughout the duration of the study, ◆ Systemic corticosteroids during the month prior to inclusion and throughout the duration of the study. − Injection of steroids in the hand during the 3 months prior to inclusion or at another site during the month prior to inclusion and throughout the duration of the study. − Treatment with: ◆ Oral anticoagulant, heparin, platelet anti-aggregant (including low-dose aspirin), thrombolytic agent, ◆ Potassium salts, potassium-sparing diuretic, ACE inhibitor, angiotensin II inhibitor, beta blocker, ◆ Methotrexate, cyclosporin, tacrolimus, trimethoprim, ◆ Lithium, ◆ Physical or alternative therapy (orthotics, acupuncture, homeopathy, physiotherapy, mesotherapy) for the current acute episode of hand osteoarthritis. ▪ Pregnant woman or nursing mother or woman of childbearing potential and sexually active not using a recognised medically effective method of contraception. ▪ Participation in a biomedical research study during the two months prior to inclusion in this study.
Tested product	**Ketum® 2.5% gel:** 3 applications a day Batch no:
Reference product:	**Oral diclofenac**: 2 capsules 3 times a day Batch no.:
Duration of therapy	7 days
Endpoints	***Efficacy*** *Primary endpoint*: Change at the end of treatment in overall spontaneous pain during the last 24 hours in the hand initially the most painful, measured on a horizontal VAS scale scored from 0 mm (left end: "absence of pain") to 100 mm (right end: "extreme pain, very intense") [5] *Secondary endpoints*: ▪ Change between D1 and D3 in overall spontaneous pain during the last 24 hours in the hand initially the most painful, measured on a VAS scale. ▪ Change between D1 and D3 and at the end of treatment in Dreiser's functional index for arthropathies of the hand [3]. ▪ Overall assessment of efficacy of treatment at the end of study visit (D7 or early discontinuation) by the patient based on a 4-point verbal rating scale: "Very effective", "Effective", "Moderately effective", "Not effective at all" ▪ Change during treatment of pain in the hand initially the most painful during the last 24 hours, evaluated daily from D1 to D7 by the patient by a score of 0 (no pain) to 10 (extreme pain) in a self-evaluation diary [5].

Laboratoire MENARINI France	**Reference to part IV**	**For national authority use only**
Name of medicinal product: Ketum® 2.5% gel	**Volume:**	
Name of active substance: ketoprofen	**Pages:**	

Endpoints (continued)

Secondary efficacy endpoints (continued)

- Clinical Global Impression (CGI3), evaluated by the doctor at the end of study visit (D7 or early discontinuation). This endpoint allowing to qualitatively assess the benefit / risk ratio is both an efficacy and safety endpoint [6].
- Assessment of compliance with treatment by calculation of the percentage compliance (ratio of total dose taken over theoretical total dose for the actual duration of treatment) of capsules and gel.

Safety

Frequency, type, severity and causal relationship of adverse events spontaneously reported by the patient or observed by the investigator during treatment.

Statistical methods:

Analysis of the primary endpoint: if the 95% confidence interval of the difference Ketum® 2.5% gel-oral diclofenac of the means of changes (value at the end of treatment – value at D1) in the VAS for pain, adjusted to the value at D1, is within the equivalence interval [-8.0; +8.0], equivalence of the effects of the two treatments is demonstrated. Primary analysis on the Per protocol population and secondary analysis on the FAS population.

Analysis of secondary endpoints: ANCOVA (adjustment to the value at D1) for quantitative criteria, Wilcoxon's two-sided test for ordinal semi-quantitative criteria, Chi square test for non-ordinal qualitative criteria.

Summary – Conclusion

POPULATIONS

	Ketum® 2.5% gel	oral diclofenac	Total
Included (randomised)	198	200	398
Safety	197	200	397
FAS	195	200	395
Per protocol	164	170	334

	Ketum® 2.5% gel	oral diclofenac	Total
Early discontinuations	11	4	15
Adverse event	7	3	10
Inadequate efficacy	1	1	2
Patient's decision	1	0	1
Non-medical reasons	2	0	2

Characteristics at inclusion (FAS population)

		Ketum® 2.5% gel	oral diclofenac	Total FAS
Sex	Men	57 (29.2%)	46 (23.0%)	103 (26.1%)
	Women	138 (70.8%)	154 (77.0%)	292 (73.9%)
Age (years)	mean ± sd	60.7 ± 8.9	61.1 ± 8.5	60.9 ± 8.7
	range	43; 82	35; 84	35; 84
Duration of acute episode (d)	mean ± sd	3.6 ± 1.1	3.7 ± 1.2	3.7 ± 1.1
Duration of 1st episode (years)	mean ± sd	5.17 ± 5.41	5.15 ± 5.35	5.16 ± 5.37
No. of acute episodes in 12 months	mean ± sd	3.7 ± 3.7	3.8 ± 3.5	3.7 ± 3.6
Family history		110 (56.4%)	100 (50.0%)	210 (53.2%)
Occupation promoting the disorder		88 (45.1%)	92 (46.2%)	180 (45.7%)
Manual activities promoting the disorder		95 (48.7%)	95 (47.7%)	190 (48.2%)
Other osteoarthritis sites		147 (75.4%)	148 (74.0%)	295 (74.7%)
Previous or concomitant disorders		167 (85.6%)	178 (89.0%)	345 (87.3%)
VAS for pain (mm)	mean ± sd	69.6 ± 11.4	70.0 ± 12.2	69.8 ± 11.8
	median (range)	70 (43; 93)	71 (45; 100)	71 (43; 100)
Dreiser's index	mean ± sd	12.5 ± 4.5	12.4 ± 4.4	12.5 ± 4.4
	median (range)	12 (5; 24)	12 (5; 26)	12 (5; 26)

The two treatment groups were comparable for characteristics of patients at inclusion in the two analysis populations.

Laboratoire MENARINI France	**Reference to part IV**	**For national authority use only**
Name of medicinal product: Ketum® 2.5% gel	**Volume:**	
Name of active substance: ketoprofen	**Pages:**	

Summary – Conclusion (continued)

MONITORING OF TREATMENT

Duration of ingestion of capsules and duration of application of gel were comparable in the two treatment groups with their median values being equal (6.67 days).

RESULTS FOR EFFICACY

Primary endpoint: change in VAS for pain at the end of treatment

In the Per protocol population

		Ketum® 2.5% gel (n=164)	oral diclofenac (n=170)	Total PP (n=334)
VAS at D1	mean ± sd	69.5 ± 11.4	70.4 ± 11.9	70.0 ± 11.7
	median (range)	70 (45; 93)	71 (45; 100)	71 (45; 100)
VAS end of treatment	mean ± sd	36.3 ± 20.1	33.6 ± 20.5	34.9 ± 20.3
	median (range)	35.5 (0; 100)	31.0 (0; 81)	33.0 (0; 100)
Delta	mean ± sd	-33.2 ± 21.0	-36.9 ± 21.0	-35.1 ± 21.1
	median (range)	-31.5 (-84; 22)	-35.0 (-91; 13)	-33.0 (-91; 22)
Adjusted difference ± Standard error		3.1 ± 2.2		
Confidence interval of the adjusted difference		**[-1.1; 7.4]**		

The 95% confidence interval of the intergroup difference (Ketum® 2.5% gel-oral diclofenac) of the means of changes adjusted to the value of VAS at D1 is within the equivalence interval [-8.0; +8.0]: equivalence of this analgesic effect of the two treatments is demonstrated.

In the FAS population

		Ketum® 2.5% gel (n=195)	oral diclofenac (n=200)	Total FAS (n=395)
VAS at D1	mean ± sd	69.6 ± 11.4	70.0 ± 12.2	69.8 ± 11.8
	median (range)	70 (43; 93)	71 (45; 100)	71 (43; 100)
VAS end of treatment	mean ± sd	37.6 ± 20.5	33.6 ± 20.5	35.4 ± 21.1
	median (range)	37.0 (0; 100)	30.5 (0; 96)	33.0 (0; 100)
Delta	mean ± sd	-32.0 ± 21.0	-36.7 ± 22.4	-34.4 ± 21.8
	median (range)	-30.0 (-84; 22)	-35.5 (-91; 37)	-33.0 (-91; 37)
Adjusted difference ± Standard error		4.4 ± 2.1		
Confidence interval of the adjusted difference		**[0.4; 8.5]**		

The 95% confidence interval of the intergroup difference (Ketum® 2.5% gel-oral diclofenac) of the means of changes adjusted to the value of VAS at D1 is not within the equivalence interval [-8.0; +8.0]. The analysis does not allow to conclude in the equivalence of the analgesic effect of the two treatments.

Secondary endpoints

In the Per protocol population:

A statistically significant difference was demonstrated in support of oral diclofenac for the therapeutic index CGI3 (2.86 ± 1.00 during treatment with Ketum® 2.5% gel and 3.09 ± 0.97 during treatment with oral diclofenac - p=0.033), but the observed difference (7%) is below the limit of 10% generally recognised to accept non inferiority.

In the FAS population:

A statistically significant difference in support of oral diclofenac was demonstrated for:

- Decreasing pain at D3 (-18.9 ± 14.8 mm during treatment with Ketum® 2.5% gel versus -22.1 ± 17.0 mm during treatment with oral diclofenac - p=0.047).
- A decrease in Dreiser's functional index at the end of treatment (-5.7 ± 4.5 during treatment with Ketum® 2.5% gel versus -6.5 ± 4.4 during treatment with oral diclofenac - p=0.027)
- The therapeutic index CGI3 (2.82 ± 1.02 during treatment with Ketum® 2.5% gel versus 3.04 ± 1.00 during treatment with oral diclofenac - p=0.019)
- The area under the curve over time of pain evaluated by the patient from D1 to D7 (31.8 ± 8.8 with Ketum® 2.5% gel versus 28.9 ± 9.6 with oral diclofenac - p=0.003).

The observed differences between the two treatments for the therapeutic index (7%) and for the area under the curve of pain intensity (10%) did not exceed the recognised limit of 10% to accept non inferiority, even though the differences observed for change in VAS at D3 (14.5%) and change at the end of treatment in Dreiser's index (12.3%) were greater than 10%.

Laboratoire MENARINI France	**Reference to part IV**	**For national authority use only**
Name of medicinal product: Ketum® 2.5% gel	**Volume:**	
Name of active substance: ketoprofen	**Pages:**	

RESULTS FOR SAFETY

The frequency of adverse events did not differ significantly in the two treatment groups:

	Ketum® 2.5% gel (n=197)	oral diclofenac (n=200)	Comparison Test of Chi²
Emergent AE (EAE)	17 (8.6%)	8 (4.0%)	p=0.058
EAE related to the study treatment	14 (7.1%)	7 (3.5%)	p=0.108
EAE which resulted in discontinuation of treatment	7 (3.6%)	3 (1.5%)	p=0.218
Serous adverse event	1 (0.5%)	0 (0.0%)	p=0.994
Gastro-intestinal (GI) EAE	12 (6.1%)	6 (3.0%)	p=0.139
Cutaneous EAE	3 (1.5%)	1 (0.5%)	p=0.605

The majority of events reported were considered related to the study treatment by the investigator: 19/23 events which occurred in 14 patients (7.1%) with Ketum® 2.5% gel (7 gastralgia, 1 nausea, 1 dyspepsia, 1 gastro-œsophageal reflux, 1 constipation, 1 acceleration of GI motility, 1 rash, 1 erythematous rash, 1 burning sensation, 1 malaise, 1 epistaxis, 1 myalgia, 1 insomnia) and 10/12 events which occurred in 7 patients (3.5%) with oral diclofenac (4 gastralgia, 1 nausea, 1 diarrhoea, 1 dry skin, 1 facial oedema, 1 cough , 1 dysgueusia).

Events which resulted in discontinuation of treatment were 3 gastralgia, 1 case of nausea, 1 erythematous rash, 1 epistaxis, and 1 wrist fracture in the Ketum® 2.5% gel group and 2 gastralgia, 1 case of nausea, 1 facial oedema, 1 cough and 1 dysgueusia in the oral diclofenac group.

Only one serious adverse event not related to treatment occurred during the study: a wrist fracture subsequent to a fall in the Ketum® 2.5% gel group.

In this study comparing Ketum gel® 2.5%, at a dosage of 3 applications a day for 7 days, to oral diclofenac, at a dosage of 50 mg 3 times a day, in treatment of painful symptoms of hand osteoarthritis, in 398 patients, the equivalence of the analgesic effect of Ketum® 2.5% gel to that of oral diclofenac was demonstrated in the Per protocol population. Analysis of secondary endpoints did not demonstrate a statistically significant and clinically significant difference between the two treatments in this population. In the FAS population, the equivalence of the analgesic effects of Ketum® 2.5% gel and oral diclofenac was not demonstrated.

The frequency and type of adverse events which correspond to the safety profile of NSAIDs were similar in the two groups. These were mainly gastrointestinal side effects (6.1% with Ketum® 2.5% gel, 3.0% with oral diclofenac). Local skin effects were reported in three patients who received Ketum gel® and one patient who received oral diclofenac.

Date of report:	20 January, 2009