# Calprotectin

Universal kit

CALPROGOLD™

**Order references**

*Reagents*

| REF | | CONT |
|---|---|---|
| CACOL-B00 | *Universal kit* | 1 x 18 mL R1 + 1 x 7.5 mL R2 |
| CACOL-H00 | *Universal kit* | 3 x 18 mL R1 + 3 x 7.5 mL R2 |
| CACOL-L00 | *Universal kit* | 7 x 18 mL R1 + 7 x 7.5 mL R2 |

*Other necessary products*

| REF | | CONT |
|---|---|---|
| CAREK-000 | *Calprotectin Calibrators Kit (6 Levels)* | 6 x 1 mL |
| CACOS-002 | *Calprotectin Low Control* | 1 x 2 mL |
| CACON-002 | *Calprotectin Medium Control* | 1 x 2 mL |
| CACOX-002 | *Calprotectin High Control* | 1 x 2 mL |
| SDBUF-B00 | *Sample Dilution Buffer* | 2 x 70 mL |
| SDBUF-H00 | *Sample Dilution Buffer* | 8 x 70 mL |
| SDBUF-L00 | *Sample Dilution Buffer* | 16 x 70 mL |

## Intended use

CALPROGOLD in vitro diagnostic reagent is used for measuring in human stool, concentration of faecal Calprotectin, a neutrophilic protein that is a marker of mucosal inflammation. CALPROGOLD can be used as an in vitro diagnostic aid in the diagnosis of inflammatory bowel disease (IBD): Chron's disease and ulcerative colitis, to differentiate between IBD from irritable bowel syndrome (IBS), to determine disease activity and monitor response to treatment in patients with IBD.

## Medical benefit - Scientific validity

Various types of organic diseases in the gastrointestinal tract may cause damage to the intestinal epithelial lining (mucosa layer). Such damage may vary from increased permeability of the mucosa to inflammation and ulcerations. The bowel content is rich in bacteria and other microorganisms releasing substances which may be toxic or chemotactic, i.e. they stimulate leukocytes, in particular polymorphonuclear neutrophilic granulocytes (PMN), to migrate into the gut lumen where they release their contents including antimicrobial substances like Calprotectin. This protein constitutes about 60% of total proteins in the cytoplasm of PMNs [2)] and can be reliably estimated in faecal samples stored for up to seven days at ambient temperature [3)].

Calprotectin is a 36 kilodalton calcium and zinc-binding protein [4)], produced by PMNs, monocytes and squamous epithelial cells (except those in normal skin) [5,6)]. After binding of calcium, it can resist degradation by leukocytic and microbial enzymes [3,7)]. By competing with different enzymes for limited, local amounts of zinc, Calprotectin can inhibit many zinc-dependent enzymes [8)] and thereby kill microorganisms or animal and human cells in culture [9,10)]. Different types of disease, for instance bacterial infections, rheumatoid arthritis and cancer, lead to activation of PMNs and increased levels of Calprotectin in plasma, cerebrospinal fluid, synovial fluid, crevicular fluid, urine or other human materials [1)].

It is of special importance that the concentration of Calprotectin in faeces is correlated with the number of PMNs migrating into the gut lumen [11)], and that it can be detected reliably even in small (less than one gram) random stool samples [3,12)]. Furthermore, organic diseases of the bowel give a strong Calprotectin signal, i.e. elevations are regularly five to several thousand times the upper reference in healthy individuals [3,13,14,15)], indicating intestinal inflammation.

Inflammatory bowel diseases (IBD), i.e. ulcerative colitis and Crohn's disease, may appear from early childhood to late adulthood and the diagnosis is often delayed due to vague symptoms or reluctance to perform endoscopy and biopsy. The CALPROGOLD calprotectin measurement can contribute to an earlier diagnosis of IBD since the test is usually positive in active IBD.

Functional disorders like irritable bowel syndrome (IBS) do not give increased faecal Calprotectin concentrations, but organic abdominal disorders like IBD do. Patients with organic and functional abdominal disorders may have similar symptoms, and clinical examination alone may not be sufficient to give a specific diagnosis. Further diagnostic procedures are complex, expensive and may expose the patient to pain and other risks. A test for faecal Calprotectin is a simple, non-invasive, inexpensive and objective method that can help selecting patients for additional examination like endoscopy. Abdominal symptoms are very common both



CE

in children and adults and a negative result as measured by the CALPROGOLD calprotectin kit can with high probability rule out inflammatory bowel disorders [13].
Mucosal healing is the optimal goal for IBD treatment, and a test for faecal Calprotectin can tell when this has been achieved. Many IBD patients in clinical remission with normal C-reactive protein (CRP) levels still have on-going inflammation [16], reflected by increased faecal Calprotectin. Such patients have increased risk of relapse within a few months [17]. If mucosal healing can be achieved, the risk of relapse and need for major abdominal surgery will be reduced [18,19]. Normalisation of Calprotectin levels means that mucosal healing has been achieved [20]. The risk and severity of side effects to treatment should be balanced against the risk of continued inflammation, severe clinical relapse and complications.
The importance of achieving mucosal healing has been the focus of many scientific reviews [21-29] and articles [30-35].

## Method principle

The calprotectin assay is performed using the CALPROGOLD Calprotectin Reagent Kit and the CALPROGOLD Calprotectin Calibrators Kit on automatic biochemistry analysers. A homogeneous immunoturbidimetric gold particle enhanced technique is used. A 2 incubations reactional steps are performed using a buffer reagent 1 and a gold colloidal probe reagent 2. The gold probe binds specifically antibodies to calprotectin inducing a specific agglutination of the gold probe. This agglutination can be monitored at 600 nm on biochemistry analysers or photometers using an endpoint protocol.

| Test type | Dilution of the sample | Reaction diluted sample volume | Buffer Reagent 1 volume | Incubation time | Gold reagent 2 volume | Reading OD 1 (Primary / Secondary) | Incubation time | Reading OD 2 (Primary / Secondary) |
|---|---|---|---|---|---|---|---|---|
| ENDPOINT | 10x | 20 µl | 180 µl | 5 minutes | 75 µl | 600 nm / 546 nm | 5 minutes | 600 nm / 546 nm |

## Warning and precautions

- For in vitro diagnostic use only.
- Must be handled by qualified personnel under the responsibility of a biologist.
- The human-origin products have been screened and found negative for HIV 1 and 2 antibodies, HCV antibodies and HBAg, but they must nevertheless be handled as potentially infectious products.
- These products contain sodium azide. Products containing sodium azide must be handled with care: avoid ingestion and contact with the skin or mucous membranes.
- Sodium azide becomes explosive on contact with heavy metals such as copper or lead.

## Samples

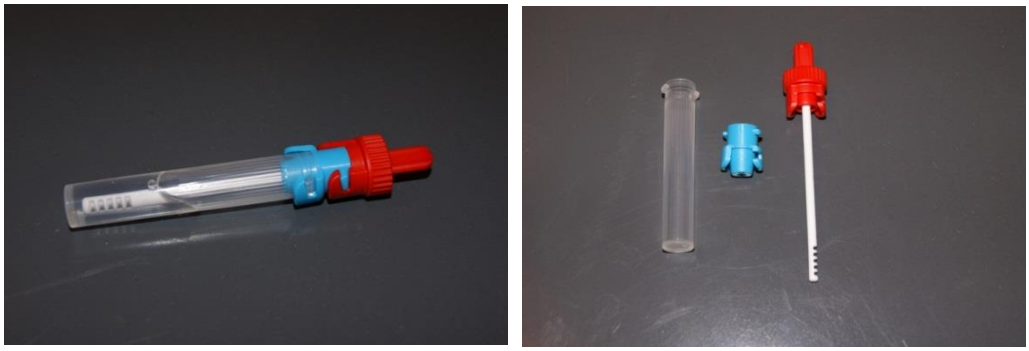
### Collection conditions

Collect specimens using standard laboratory techniques; use only suitable procedures, tubes, or collection containers.

Since Calprotectin is very stable in stools, patients can collect small faecal samples at home.
Collect 1 – 5 g (approximately one teaspoonful), place it in a suitable clean container and deliver it to the laboratory as soon as possible but within four days. When put in a container approved for transport, it can be sent by ordinary mail, i.e. no refrigeration is needed. Exposure to temperatures above 25°C should be avoided.
Samples can also be stored frozen, at -20°C or lower, until delivery or mailing. Frozen samples must be thawed and equilibrated to room temperature before extraction and testing. Note that freezing faecal samples can in some cases result in increased Calprotectin levels, most likely due to release from granulocytes.
*Note:* Before commencing extraction, the stool sample should be homogenised well using for example a spatula, before the small amount for extraction is taken out.
For extraction we recommend the use of Calpro EasyExtract™ according to package insert. Other methods and devices, validated by the customer, can be used.

- Extraction using the Calpro EasyExtract™

Instructions for use: please read package insert for product No. CAL0510



(Calpro AS, Product No. CAL0510)

### Sample type

Faecal samples

### Storage and stability of specimens

- Before extraction :

| Temperature | Stability |
|---|---|
| 2 – 25°C | 5 days |
| - 20 °C | 2 years |

This information comes from data originating from internal measurements.

- After extraction with Calpro EasyExtract™ :

| Temperature | Stability |
|---|---|
| 2 – 8°C | 7 days |
| 8 – 25°C | 5 days |

This information comes from data originating from manufacturer of the device (see Calpro EasyExtract™ instruction for use).

## Reagents

### Composition and concentrations/Storage

Active components:
Reagent R1: none
Reagent R2: Suspension of colloidal gold particles coated with monoclonal human calprotectin antibodies (mouse).

Other components:
Reagent R1: buffer, stabiliser, inorganic salt and preservative.
Reagent R2: buffer, inorganic salt and preservative.

Conservation temperature:
Reagent R1: 2 - 8 °C.
Reagent R2: 2 - 8 °C.

### Preparation

Ready to use.

R1 and R2 must have the same lot number for their use.

### Storage and stability

Reagents are stable until the expiration date printed on the packaging (months passed), under the following recommended storage and handling conditions:

- Unopened vial stored at temperature indicated on packaging.
- Opened vial: closed immediately after use or placed on closed analyser intended for this purpose, not contaminated by handling and stored at the temperature indicated on the packaging.

Reagents are shipped at 2-8°C.

Note:

- Do not freeze the reagents.
- Nanoparticle-based reagents can settle over time. It may be necessary to delicately mix by repeated turning.

### Other materials required

Usual laboratory equipment including an analytical system equipped with a photometric detector.

## Calibration

### Calibration

The calibration curve is performed by using the calibration kit indicated in the “Order references” section.

### Traceability

The method has been standardised with a benchmark method traceable to the CALPROLAB™ Calprotectin ELISA (ALP) as described in the associated calibrators data sheet (see the “Order references” section).
Calibrate the method when the reagent batch number changes or in case of change in performance (contact the manufacturer if the changes persist) or if quality control requires it.

## Quality control

The frequency of controls and the confidence limits must be adapted to the laboratory requirements. The results must be within the defined confidence limits. Each laboratory shall establish corrective measures to be taken if results fall outside the defined limits. Comply with current legislation in the country and local guidelines relating to quality control.
The calibration curve and its stability must be validated using the control materials indicated in the “Order references” section**.**

## Reference values

| | Reference values |
|---|---|
| Normal value | 5 – 50 mg/kg |
| Positive value | > 50 mg/kg |
| Median value in patients with symptomatic colorectal cancers | 350 mg/kg |
| Active, symptomatic inflammatory bowel disease | 200 – 40.000 mg/kg |

International units: mg/kg
Conventional units: µg/g

This information coming from data originating from “Røseth AG et al.: Assessment of the neutrophil dominating protein calprotectin in faeces. Scand J Gastroenterol 1992; 27: 793-798.” And “Johne B et al.: A new fecal calprotectin test for colorectal neoplasia, Scand J Gastroenterol 2001; 36: 291-296“.

Each laboratory must check the validity of its values and if necessary establish its own reference values, depending on the population examined.

## Analytical performances

The analytical performance data below are given as an indication. The results obtained in the laboratory may differ from these.

### Linearity

Low linearity was assessed according to Clinical and Laboratory Standards Institute (CLSI) protocol EP06-A, with dilution of high faecal extract in sample dilution buffer. The method has been demonstrated to be linear from 32.4 mg/kg, with an acceptance criterion of 20% of allowable nonlinearity.
High linearity was assessed according to Clinical and Laboratory Standards Institute (CLSI) protocol EP06-A, with dilution of high faecal extract in sample dilution buffer. The method has been demonstrated to be linear up to 802.0 mg/kg, with an acceptance criterion of 20% of allowable nonlinearity.

Linearities were also evaluated with a dilution of a high faecal extract in a low faecal extract. In this case, the method has been determined to be linear from 31.4 mg/kg to 712.1 mg/kg, with an acceptance criterion of 20% of allowable nonlinearity.

### Measurement range

32.4 mg/kg – 802.0 mg/kg.
The measurement range is bounded by the low and high linearity limits. Samples having a concentration lower than the lower limit must be concentrated. Samples having a concentration greater than the upper limit must be diluted.

### Lower limits of measurement

Limit of Blank = 9.7 mg/kg
Limit of Detection = 16.9 mg/kg
Limit of Quantification = 21.4 mg/kg
The Limit of Blank was determined in accordance with the CLSI EP17-A2 requirements, based on 60 determinations of blank samples. The Limit of Blank is the 95th percentile of the standard normal distribution of the blank samples determination.
The Limit of Detection was determined in accordance with the CLSI EP17-A2 requirements and with a proportion of false positive (α) less than 5 % and false negative (β) less than 5 %, based on 120 determinations with 60 blank and 60 low level replicates.
The Limit of Quantitation was determined in accordance with the CLSI EP17-A2 requirements for the functional sensitivity determination, based on 80 determinations of 7 low levels during 20 days and with a %CV goal of 20 %.

### Interferences (Analytical specificity)

No interference for :

- Prednisolon (0.05 mg/100mg)
- Imurel (0.25mg/100mg)
- Salazopyrin (1.95mg/100mg)
- Trimetoprim (0.3mg/100mg)
- Ciprofloxacin (1.17mg/100mg)
- Pentasa (3.1mg/100mg)
- Asacol (1.8mg/100mg)
- Ibux (2.5mg/100mg)
- Multivitamin (0.5mg/100mg)
- Blood Human Hemoglobin (3mg/100mg)
- Bacteria cultures at concentration of $10^8$/100mg (*Citrobacter freundii, Escherichia coli, Klebsiella pneumonia, Salmonella enterica, Yeirsina enterolitica*)

All interference studies are performed at 4 calprotectin levels (~50mg/kg; ~90mg/kg; ~275mg/kg; ~1100mg/kg).

### Precision

Precision was evaluated with 3 quality controls and 4 faecal extracts samples following the CLSI protocol EP05-A3. Within-run precision was determined using 2 runs per day with 2 replicates per run. Within-lab precision was determined using a single lot of reagent and at least 4 calibrations. These results are guidelines. Variables (e.g. instrument maintenance, environment, sample handling) can affect the reproducibility of test results.

| | Number of days | Number of measures | Mean concentration | Within-run CV | Within-lab CV |
|---|---|---|---|---|---|
| Control 1 | 22 | 88 | 95.8 mg/kg | 4.8 % | 8.2 % |
| Control 2 | 22 | 88 | 475.8 mg/kg | 3.5 % | 7.3 % |
| Control 3 | 22 | 88 | 1320.3 mg/kg | 6.4 % | 7.3 % |
| Sample 1 | 22 | 88 | 66.9 mg/kg | 3.1 % | 11.5 % |
| Sample 2 | 22 | 88 | 221.4 mg/kg | 2.4 % | 9.9 % |
| Sample 3 | 22 | 88 | 553.6 mg/kg | 3.0 % | 6.5 % |
| Sample 4 | 22 | 88 | 1003.5 mg/kg | 2.5 % | 4.1 % |

## Limitations of the method

The results of this test should always be interpreted in relation to the patient's medical history, clinical signs and other findings.

### Prozone

By limiting the linearity to the value of the upper limit of the measurement range, no excess antigen effect was observed for samples with a concentration up to 10.000 mg/kg.

### Matrix effect

Results shown no matrix effect. The inter-laboratory control samples and controls can yield different results from those obtained with other assay methods because there is no international standardized method. Each manufacturer will use internal method for calibrator value assignment. In this case, an analysis of the results according to specific target values of the method utilised may be necessary. If in doubt, contact the manufacturer.

## Utilisation procedure

Validated automatic applications for different analyzers are available from DiAgam. The utilisation procedure indicated below enables deriving a manual or automatic application of the reagent (NB - comply with the sample/R1/R2 ratios correctly). Please contact the manufacturer for more information.

Mix 20 µl of sample (diluted 10 time by the analyser 10µl + 90µl of sample dilution buffer) with 180 µl of reagent R1 and incubate the mixture for 5 minutes at 37°C. Then add 75µl of reagent R2 to the reaction mix, read the optical density at a wavelength of 600 nm (primary wavelength) (OD1 600 nm) and at a wavelength of 546 nm (secondary wavelength) (OD1 546 nm). After new incubate at 37°C for 5 min, perform a second OD measurement at 600 nm (OD2 600 nm) and 546 nm (OD2 546 nm).

In order to obtain the final OD of the sample, it is first necessary to calculate the intermediate ODs as indicated in the following equations:

OD1 intermediate=OD1 (600 nm)-OD1 (546 nm)

OD2 intermediate=OD2 (600 nm)-OD2 (546 nm)

The final OD is finally calculated as shown in the following equation:

OD final=OD2 intermediate-f x OD1 intermediate

Where f is a factor taking account of the difference in volume between the 2 measurements of OD.

The final OD of the "reagent blank" sample as well as the known calibrator concentrations allows a calibration curve to be drawn. The transfer of the OD measured for an unknown sample on this calibration curve enables its concentration to be determined.

## Literature

1. Johne B et al.: Functional and clinical aspects of the myelomonocytic protein calprotectin. J Clin Pathol: Mol Pathol 1997; 50:113-123.

2. Fagerhol MK et al.: Calprotectin (The L1 leukocyte protein) in: Smith VL and Dedman JR (eds): Stimulus response coupling: The role of intracellular calcium-binding proteins. CRC Press, Boca Raton 1990, p. 187-210
3. Røseth AG et al.: Assessment of the neutrophil dominating protein calprotectin in faeces. Scand J Gastroenterol 1992; 27: 793-798.
4. Dale I et al.: Purification and partial characterization of a highly immunogenic human leukocyte protein, the L1 antigen. Eur J Biochem 1983;134: 1-6.
5. Dale I et al.: Distribution of a new myelomonocytic antigen (L1) in human peripheral blood leukocytes. American J of Clin Pathology 1985; 84: 24-34
6. Brandtzaeg P et al.: Distribution of a formalin-resistant myelomonocytic antigen (L1) in human tissues. II. Normal and aberrant occurrence in various epithelia. American J of Clin Pathology 1987; 87: 700-707.
7. Fagerhol MK: Nomenclature for proteins: is calprotectin a proper name for the elusive myelomonocytic protein? J Clin Pathos: Mol Pathos 1996; 49: M74-M79.
8. Isaksen B and Fagerhol MK: Calprotectin inhibits matrix metalloproteinases by sequestration of zinc. J Clin Pathol: Mol Pathol 2001; 54: 289-292.
9. Steinbakk M et al.: Antimicrobial actions of calcium binding leukocyte L1 protein, calprotectin. Lancet 1990; 336: 763-765.
10. Yui S et al.: Induction of apoptotic cell death in mouse lymphoma and human leukaemia cell lines by a calcium-binding protein complex, calprotectin, derived from inflammatory peritoneal exudates cells. Journal of Leukocyte Biology 1995; 58: 650-658.
11. Røseth AG et al.: Correlation between faecal excretion of Indium-111-labelled granulocytes and calprotectin, a granulocyte marker protein, in patients with inflammatory bowel disease. Scand J Gastroenterol 1999; 34: 50-54
12. Tøn H et al.: Improved assay for fecal calprotectin. Clinica Chimica Acta 2000; 292: 41-54.
13. Tibble J et al.: A simple method for assessing intestinal inflammation in Crohn's disease. Gut 2000; 47: 506-513.
14. Bunn SK et al.: Fecal calprotectin: Validation as a non-invasive measure of bowel inflammation in childhood inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2001;33: 14-22.
15. Bjarnason I and Sherwood R: Fecal calprotectin: A significant step in the noninvasive assessment of intestinal inflammation. J Paediatric Gastroenterology Nut 2001; 33: 11-13
16. Siegmund B et al.: [What has been confirmed in the treatment of inflammatory bowel disease?]. Internist 2010;51:1492-1498
17. Tibble JA et al.: Surrogate markers of intestinal inflammation are predictive of relapse in patients with inflammatory bowel disease. [Journal Article] Gastroenterology 2000; 119(1):15-22.
18. Schnitzler F et al.: Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. Inflamm Bowel Dis 2009;15:1295-1301
19. Björkesten CG et al.: Endoscopic monitoring of infliximab therapy in Crohn's disease. Inflamm Bowel Dis. 2010, Sep 21
20. Røseth AG et al.: Assessment of disease activity in ulcerative colitis by faecal calprotectin, a novel granulocyte marker protein. Digestion 1997; 58:176-80
21. Devlin SM and Panaccione R: Evolving inflammatory bowel disease treatment paradigms: top-down versus step-up. Med Clin North Am. 2010;94:1-18
22. Pineton de Chambrun G et al.: Clinical implications of mucosal healing for the management of IBD. Nat Rev Gastroenterol Hepatol 2010; 7(1):15-29
23. Lichtenstein GR and Rutgeerts P: Importance of mucosal healing in ulcerative colitis. Inflamm Bowel Dis. 2010;16:338-346
24. Smith MA et al.: Pharmacogenomics in the treatment of inflammatory bowel disease. Pharmarcogenetics, 2010;11(3):421-437
25. Lin MV et al.: What is the optimal therapy for Crohn's disease: step-up or top-down? Expert Rev Gastroenterol Hepatol. 2010;4(2):167-180
26. Strauch U and Schölmerich J.: Emerging drugs to treat Crohn's disease. Expert Opin Emerg Drugs, 2010;15(2):309-322
27. Isaacs KL: How rapidly should remission be achieved? Dig Dis 2010;28(3):548-555
28. Schwartz M and Regueiro M: Prevention and treatment of postoperative Crohn's disease recurrence: an update for a new decade. Curr Gastroenterol Rep. 2011 Feb;13(1):95-100
29. Ha C and Kornbluth A: Mucosal healing in inflammatory bowel disease: where do we stand? Curr Gastroenterol Rep. 2010;12(6):471-478.
30. Fagerberg UL et al.: Fecal calprotectin: a quantitative marker of colonic inflammation in children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2007;45(4):414-420
31. Rutgeerts P et al.: Biological therapies for inflammatory bowel diseases. Gastroenterology, 2009;136(5):1182-1197
32. Jalocha L et al.: Mucosal healing in Crohn disease. Pol Merkur Lekarski. 2009;26(155):554-555;

33. Baert F et al.: Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. Gastroenterology, 2010;138(2):463-468
34. Allez M and Lémann M: Role of endoscopy in predicting the disease course in inflammatory bowel disease. World J Gastroenterol. 2010;16:2626-2632
35. Lasson A: Calprotectin in feces a well-documented marker of gastrointestinal inflammation. Indicates disease intensity--normalization of values predict mucosal healing. Läkartidningen, 2010;107(143):2645-2649
36. Sander J et al.: Plasma levels of the leucocyte L1 protein in febrile conditions: relation to aetiology, number of leucocytes in blood, blood sedimentation reaction and C-reactive protein. Scand J Clin Lab Invest. 1984 Jun;44(4): 357-62
37. Golden BE et al.: Calprotectin as a marker of inflammation in cystic fibrosis. Arch Dis Child. 1996 Feb;74(2):136-9
38. Berntzen HB et al.: The leukocyte protein L1 in plasma and synovial fluid from patients with rheumatoid arthritis and osteoarthritis. Scand J Rheumatol 1991; 20(2): 74-82
39. Haga HJ et al.: Calprotectin in patients with systemic lupus erythematosus: relation to clinical and laboratory parameters of disease activity. Lupus 1993; 2(1): 47-50
40. Madland TM et al.: Leukocyte protein calprotectin and outcome in rheumatoid arthritis. A longitudinal study. Scand J Rheumatol. 2002;31(6):351-354
41. Frosch M et al.: Expression of myeloid-related proteins 8 and 14 in systemic-onset juvenile rheumatoid arthritis. Arthritis Rheum 2003;48(9):2622-2626
42. Hammer HB et al. Calprotectin (a major leucocyte protein) is strongly and independently correlated with joint inflammation and damage in rheumatoid arthritis. Ann Rheum Dis 2007;66(8):1093-97
43. Arvesen K et al.: Eur Heart J. 1996 Aug;17 Abstr Suppl:1-646.
44. Katashima et al.: Enhanced expression of the S100A8/A9 complex in acute myocardial infarction patients. Circ Journal 2010;74(4):741-8
45. Altwegg LA et al.: Myeloid-related protein 8/14 complex is released by monocytes and granulocytes at the site of coronary occlusion: a novel, early, and sensitive marker of acute coronary syndromes. European Heart Journal 2007;28(8):941-8
46. Johne B et al.: A new fecal calprotectin test for colorectal neoplasia, Scand J Gastroenterol 2001; 36: 291-296

## Symbols legend

The following symbols may appear on the packaging and the label:

| | | | |
|---|---|---|---|
| LOT | *Batch code* | BUF | *Buffer* |
| | *Use until* | CAL | *Calibrator* |
| | *Manufacturer* | H | *High* |
| IVD | *In vitro diagnostic medical device* | M | *Moderate* |
| | *Temperature (Storage at)* | L | *Low* |
| REF | *Catalogue reference* | 4 LEV | *4 levels* |
| | *Read the usage instructions* | 5 LEV | *5 levels* |
| REAG | *Reagent* | 6 LEV | *6 levels* |
| KIT | *Kit* | CONTROL | *Control* |
| CONT | *Content* | CE | *This product meets the requirements of European Directive 98/79 EC concerning in vitro diagnostic medical devices* |
| Ab | *Antibody or Antisera* | | Track version changes |

| | |
|---|---|
| *DiAgam Headquarters* | *DiAgam Belgium: Rue du Parc Industriel 40, 7822 Ghislenghien, Belgium*<br>*Avenue Louis Lepoutre 70, 1050 Bruxelles, Belgium* |

| | |
|---|---|
| *Distributed by :* | *DiAgam SA, Avenue Louis Lepoutre 70, 1050 Bruxelles, Belgium, and its authorized representatives. www.diagam.com*<br>*Calpro AS, Arnstein Arnebergs vei 30, 1366 Lysaker, Norway, and its authorized representatives. www.calprogold.com* |