microRNA Research
miRCURY™ LNA Products

- microRNA Knockdown
- microRNA Expression Profiling
- microRNA Profiling Services
- microRNA Detection

www.exiqon.com
MicroRNA Research with miRCURY™ LNA microRNA Products

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About Exiqon
Exiqon is a leading supplier of high-value gene expression analysis products for the life sciences, research and drug discovery industries. Exiqon's rapidly growing product offerings integrate innovative chemistries with webbased software tools to help scientists achieve rapid and reliable results. Exiqon markets its products directly on www.exiqon.com, or through distributors, and partners its proprietary Locked Nucleic Acids (LNA™) and Anthraquinone (AQ-Link™) technologies through industry leaders. Exiqon is located in the Medicon Valley area of Copenhagen, Denmark and has an office in Boston, United States.

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What are microRNAs?
MicroRNAs (miRNAs) have rapidly emerged as an important class of short endogenous RNAs that act as posttranscriptional regulators of gene expression by base-pairing with their target messenger RNAs (mRNAs). In the cytoplasm of the cell, miRNAs are typically found in the mature form as 19-25 nucleotide (nt) RNAs that have been processed sequentially from longer hairpin transcripts by the RNAse III ribonucleases Drosha and Dicer.

To date more than 4000 miRNAs have been annotated in vertebrates, invertebrates and plants and many miRNAs that correspond to putative genes have also been identified. Some miRNAs have multiple loci in the genome and occasionally, several miRNA genes are arranged in tandem clusters. Recent bioinformatic predictions combined with array analyses, small RNA cloning and Northern blot validation indicate that the total number of miRNAs in the different vertebrate genomes is significantly higher than previously estimated and maybe as high as 1000.

A significant role in gene regulation
Initial studies indicate that miRNAs may regulate as much as 30% of all genes in the genome, thus comprising a totally new level of gene regulation. miRNAs have already been found to play important roles in several types of cancers and in tissue differentiation.

A representation of microRNA biogenesis

MicroRNA research
The study of miRNAs represents a new area for research of post-transcriptional control. Perturbed expression of miRNAs has been implicated in cancer and other diseased states, such as viral infection. An understanding of miRNAs appears promising as a basis for diagnostics and provides novel targets for treating disease. There is a clear need to better understand the role and significance of miRNA for control of gene expression.
Overview of miRCURY™ LNA Products

Exiqon’s miRCURY™ LNA microRNA products provide the perfect basis for studying short nucleic acid targets. The key to this is the nucleotide analog Locked Nucleic Acid (LNA™).

What is a Locked Nucleic Acid?
Locked Nucleic Acids (LNA™) are a class of nucleic acid analogues in which the ribose ring is “locked” by a methylene bridge connecting the 2’-O atom with the 4’-C atom (see structure right).

LNA™ nucleosides contain the six common nucleobases (T, C, G, A, U and mC) that appear in DNA and RNA and thus are able to form base-pairs according to standard Watson-Crick base pairing rules. Oligonucleotides incorporating LNA™ have increased thermal stability and improved discriminative power with respect to their nucleic acid targets.
LNA™ can be mixed with DNA, RNA and other nucleic acid analogs using standard phosphoramidite synthesis chemistry. LNA™ oligonucleotides can easily be labeled with standard oligonucleotide tags such as DIG, fluorescent dyes, biotin, amino-linkers, etc. Thus a very high degree of freedom in the design of primers and probes exists.

The LNA™ advantage
It has been known for a long time that LNA-based probes show particular advantageous properties when used in the detection of short RNA and DNA targets, or short sequences within larger targets. Exiqon has been able to exploit the uniquely high affinities that LNA-based probes have for miRNAs in our range of miRCURY™ LNA products for microRNA research. This technology is the basis for microRNA functional studies through miRCURY™ LNA Knockdown probes, microRNA profiling with miRCURY™ LNA Arrays, and miRNA detection through miRCURY™ LNA microRNA in situ hybridisation and Northern blot probes.
miRCURY™ LNA microRNA Knockdown probes: Confirm or determine miRNA function

At a glance:
▶ Effective and sequence-specific antisense inhibition of miRNA
▶ Minimal cytotoxicity
▶ Compatible with standard cell transfection methods
▶ Increased biological stability

Knockdown of microRNAs
Knockdown of miRNAs represents one of the most appropriate methods to determine miRNA function and the validation of putative miRNA targets. Due to the fact that miRNAs repress protein expression at the level of mRNA, knockdown of a miRNA will typically lead to an increase in target protein expression. This can be a useful tool in identifying mRNA transcripts predicted to be miRNA targets by bioinformatics.

Specific Knockdown of microRNA
Knockdown probes for miRNA need to be highly specific, effective at physiological temperatures and non-toxic.

Exiqon’s miRCURY™ LNA microRNA Knockdown technology enables sequence-specific inhibition of mature miRNAs in vitro and in vivo. LNA-based probes consistently show improved antisense efficacy and higher Tm’s towards their complementary single-stranded RNA targets compared to 2’-O-methyl oligonucleotides. Using our expertise in bioinformatics design of LNA™ probes, along with in-house research, we have optimally designed each miRCURY™ LNA microRNA Knockdown probe to be as specific for its target as possible.

The increased affinity of miRCURY™ LNA microRNA Knockdown probes means that they are effective at physiological temperature. Furthermore, they can be used at a low concentration, thus minimizing potential cytotoxic effects.

Depletion of miRNAs can be judged in a number of ways: by the decrease in signal of the target miRNA on an array, specific for miRNAs by the absence of binding of an in situ hybridisation probe, and by the decrease in hybridisation signals in Northern blots as LNA-miRNA hybrids are thermally stable in denaturing gels. De-repression of the cognate target protein expression is another indicator of successful miRNA knockdown.
**Published Research using miRCURY™ LNA Knockdown Probes**

In one of the first examples of a publication using miRCURY™ LNA microRNA Knockdown probes, Fazi *et al.* (Cell 123, 819-831), hsa-mir-223 levels were reduced two-fold using a miRCURY™ LNA microRNA Knockdown probe. This led to reduced expression of CD14+, demonstrating that hsa-mir-223 is an important modulator of human myeloid differentiation. Ørum *et al.* (Gene 372, 137-141) showed that miRCURY™ LNA-based microRNA Knockdown was used to up-regulate the expression of Hid protein in KC 167 cells from Drosophila melanogaster. Naguibneva *et al.* (Nature Cell Biology 8, 278-284), demonstrated effective knockdown of hsa-mir-181, with a demonstrable effect on myoblast differentiation.

**Product Description**

Each miRCURY™ LNA microRNA Knockdown probe is a full length complementary probe to its miRNA target. Every probe is an LNA-enhanced oligonucleotide, designed using Exiqon’s in-house design software. 5 n mole of probe is provided in RNAse-free water, allowing direct application in standard transfection protocols. Probes are available with a choice of labels: unlabeled probes are available, termed ‘Ready to label.’ This means that the probes can be enzymatically labeled with e.g., kinase or ligase.

**Product Table**

<table>
<thead>
<tr>
<th>Product no.</th>
<th>Product Description</th>
<th>Label</th>
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<tbody>
<tr>
<td>XXXXX-00</td>
<td>miRCURY™ LNA microRNA Knockdown, 5 n mole</td>
<td>Ready to Label*</td>
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<td>XXXXX-08</td>
<td>miRCURY™ LNA microRNA Knockdown, 5 n mole</td>
<td>3’-fluorescein</td>
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</table>

*“Ready to label” means that the miRCURY™ LNA microRNA Knockdown probe can be enzymatically labeled with the detection moiety of choice. For example, nucleotides labeled with DIG, radiolabel, biotin or fluorophores.

**Pre-designed miRCURY™ LNA microRNA Knockdown probes**

are available for all known miRNAs as registered and annotated in the miRNA Registry (miRBase) at The Wellcome Trust Sanger Institute (http://microrna.sanger.ac.uk/).

**Custom miRCURY™ LNA microRNA Knockdown probes**

are available for all other microRNAs and other small RNAs.

**Control miRCURY™ LNA microRNA Knockdown probes**

are available. Please go to www.exiqon.com

**Ordering:** Go to www.exiqon.com/shop. Select your miRCURY™ LNA microRNA Knockdown product by Product Number, name of microRNA (must be entered exactly as given in the Sanger miRNA registry, e.g. “hsa-mir-1”) or sequence. (For example, ordering a miRCURY™ LNA microRNA Knockdown probe for hsa-mir-1 can begin by entering 118008-00, hsa-miR-1 or UGGAAUGUAAGAGUAUGUA into the search window.)
miRCURY™ LNA Array microRNA Expression Profiling

miRCURY™ LNA Arrays:
the fastest and most accurate way for microRNA profiling

At a glance
- Tm-normalized, LNA-enhanced capture probes
- Works on just 1μg total RNA
- No need for miRNA enrichment
- Reduced sample handling
- Use less sample, get reliable results and save time

Microarrays represent one of the fastest and most comprehensive methods for determining the miRNA profile of a sample. It has been argued that the miRNA profile of a sample can be used as a 'signature' that can be used as a basis for diagnosis. The miRCURY™ LNA Array provides the ability to conduct genome-wide profiling of miRNA in samples. It can be used to identify signatures associated with cancer, tissue profiling, drug profiling, development up- and down-regulation of miRNAs.

The superior alternative to DNA-based arrays for microRNA profiling
miRCURY™ LNA Arrays have been designed to address issues faced when using DNA-based oligonucleotide capture probes for the profiling of miRNAs. Specifically, DNA-based methods require miRNA enrichment and signal amplification methods due to the lower affinity of DNA oligonucleotides for short nucleic acid targets. Furthermore, there is limited flexibility for producing a Tm-normalized capture probe set for such short targets as miRNA with DNA-based oligonucleotides.

Tm-normalized capture probes
The capture probes used in the miRCURY™ LNA Arrays use Exiqon's LNA™ design expertise to produce Tm-normalized, high affinity capture probes – Tm of 72°C - ensuring all miRNA targets hybridise to the array with equal affinity at the high-stringency hybridisation temperature of 60°C.

Profile microRNA with just 1 μg of total RNA - no need for microRNA enrichment:
miRCURY™ LNA Arrays require just 1μg of total RNA to obtain an accurate miRNA profile without miRNA enrichment saving time and reducing the possibility of losing miRNAs during sample prep. Removing the miRNA-enrichment step allows time-saving and reduces the possibility of miRNA-enrichment artefacts from affecting your data.

miRCURY™ LNA Array Workflow
1. Prepare RNA sample
   Total RNA sample (Use 1 – 10 μg, total RNA). miRNA enrichment is optional.
2. Label RNA sample with Hy3™/Hy5™ dyes.
   Uniform and robust miRNA labeling in 90 minutes
3. Hybridise overnight
4. Obtain the microRNA profile of your sample

miRCURY™ LNA Arrays require only 1 μg of total RNA to profile microRNAs
Identical miRNA profiles are produced from starting amounts of total RNA that span the range of 10μg to 1μg, without miRNA enrichment. 17 different miRNAs detected in human lung total RNA are represented. Numbers in the right hand of each box show the amount of total RNA used to produce each profile.
Published Research using miRCURY™ LNA Arrays

Castoldi et al. (RNA 12, 913-920) demonstrated the advantages of using LNA-based probes for miRNA profiling, when compared with DNA-based arrays. The paper describes how the biophysical properties of LNA were exploited to design probe sets for uniform, high-affinity hybridisations yielding highly accurate signals able to discriminate between single nucleotide differences and, hence, between closely related miRNA family members. The superior detection sensitivity eliminates the need for RNA size selection and/or amplification.

High sensitivity and dynamic range of miRCURY™ LNA Array

By using careful design rules regarding incorporation of LNA™, the miRCURY™ LNA Array capture probes have been found to be significantly more sensitive than DNA-based arrays for miRNA detection. The miRCURY™ LNA Array is capable of detecting as little as 50 attomole of miRNA.

Two pools of synthetic miRNAs (2 fmol of each miRNA) were spiked into a complex background of yeast total RNA (1 μg/μL) with hsa-miR-196a/hsa-miR-19a in one pool and hsa-miR-196b/hsa-miR-19b in the other pool. One pool was labeled with Hy3™ and the other pool was labeled with Hy5™ using the miRCURY™ LNA Array Labeling Kit. The labeling reactions were pooled and hybridized onto miRCURY™ LNA Arrays system. The perfect-match/mismatch ratios are in the range 32-1110.

Product Description

Each miRCURY™ LNA Array consists of LNA-modified capture probes specific for each miRNA target. Capture probes are Tm-normalized to 72°C. Probes are spotted onto Corning® Epoxide slides. Each array is delivered in a (vacuum) sealed package containing desiccant.

miRCURY™ LNA Arrays come in pack sizes of 3, 6 and 24 arrays. Arrays, or ready-to-spot probesets come supplied with hybridisation and wash buffers.

miRCURY™ LNA Array Spike-in miRNA Kit:

- Improve the quality of your data analysis

Available with all miRCURY™ LNA Array products, the Spike-in miRNA kit contains 10 synthetic spike-in miRNAs. The spike-in capture probes can be used

- as a control of the labeling reaction and hybridization
- as a help in deciding scanner settings between channels
- as a control of the data normalization procedure
- to estimate the variance of replicated measurements within arrays
- to assess technical variability between different parts of the array

Two pools of synthetic miRNAs (2 fmol of each miRNA) were spiked into a complex background of yeast total RNA (1 μg/μL) with hsa-miR-196a/hsa-miR-19a in one pool and hsa-miR-196b/hsa-miR-19b in the other pool. One pool was labeled with Hy3™ and the other pool was labeled with Hy5™ using the miRCURY™ LNA Array Labeling Kit. The labeling reactions were pooled and hybridized onto miRCURY™ LNA Arrays system. The perfect-match/mismatch ratios are in the range 32-1110.

The figure shows the distribution of the 10 spike-in miRNAs spiked into a total RNA sample.
At a glance:
- The perfect complement to miRCURY™ LNA Arrays
- One-step protocol
- Requires just 1 μg of total RNA
- Scalable protocol
- Uniform labeling method means all target miRNAs are labeled to the same degree without sequence bias
- Matches all common microarray scanning equipment.

Straightforward and fast microRNA labeling
The miRCURY™ LNA Array labeling kit provides a fast and simple method that allows you to label your total RNA sample and apply it directly to your microarray. There is no need for miRNA enrichment, or other time-consuming sample handling steps. When used with miRCURY™ LNA Arrays, the labeling kit allows for the labeling of down to 1μg of total RNA for use in miRNA profiling.

The kits are used for labeling of total RNA samples with Hy3™ and Hy5™ fluorophores - dyes spectrally equivalent to the well-known Cy3™ and Cy5™ fluorophores, allowing for miRNA expression patterns to be determined on standard array scanning instrumentation.

One fluorescent label per microRNA
Due to the method used in the miRCURY™ LNA Array labeling kits, only one fluorescent label is incorporated per miRNA.

The miRCURY™ LNA Array microRNA labeling kit works on plant miRNAs in addition to animal miRNAs, making it the most versatile miRNA labeling kit available.

miRCURY™ LNA Array Labeling method
The miRCURY™ LNA Array Labeling Kit requires just 1 μg of total RNA with no requirement for miRNA enrichment. The labeling protocol is 90 minutes and miRNAs are uniformly labeled.

<table>
<thead>
<tr>
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<tr>
<td>208030</td>
<td>Hy5™ labeling kit</td>
<td>miRCURY™ LNA Array, Hy5™ labeling kit (24 rxns)</td>
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<td>208031</td>
<td>Hy3™ labeling kit</td>
<td>miRCURY™ LNA Array, Hy3™ labeling kit (24 rxns)</td>
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<td>208031</td>
<td>Hy3™/Hy5™ labeling kit</td>
<td>miRCURY™ LNA Array, Hy3™/Hy5™ labeling kit (24 rxns)</td>
</tr>
</tbody>
</table>
miRCURY™ LNA Array microRNA Profiling Service

Use Exiqon’s expertise to keep your research on track

At a glance:
- Obtain reliable results fast
- Use Exiqon’s time and expertise
- Built-in controls
- Unique QC feature:
  - synthetic spike-in miRNAs
- Capture probes spotted 4 times, positive and negative controls

Speed up your microRNA research
Exiqon’s miRCURY™ LNA Array miRNA Profiling Services is designed to allow you to obtain miRNA profiles for your samples without doing more than sending us your total RNA samples and analysing your data when we send it to you. Following a check for RNA sample quality, Exiqon will take care of the steps in-between sample labeling, hybridisation to miRCURY™ LNA Arrays and data generation.

Using miRCURY™ LNA Array miRNA Profiling Services gives you access to the most advanced miRNA profiling arrays available, incorporating LNA™-based capture probes that provide the following benefits:
- Use less sample
  - Profiling using 2μg total RNA/sample/array
- Obtain results you can rely on
  - Tm-normalized capture probes with high affinity for miRNA targets
  - No miRNA enrichment required
- Save time

Use Exiqon’s expertise and advice
Each service is customized to your specific requirements, in consultation with Exiqon’s experts, who have broad experience in miRNA expression analysis.

www.exiqon.com
**miRCURY™ LNA Array microRNA Profiling Service**

Each service project is tailored to your specific requirements in consultation with Exiqon’s experts, who have broad experience in microRNA expression analysis.

We can profile miRNA expression from as little as 2μg total RNA. There is no need for microRNA enrichment.

Prior to initiating the analysis we will subject your samples to a RNA quality control to assess the integrity of the RNA, its content of small RNA, and its concentration.

Our miRCURY™ LNA Array labeling kit allows uniform labeling of microRNAs with no sequence bias. Hybridization and washing steps are fully automated for excellent reproducibility.

Arrays will be scanned and image analysis performed to quantify the signals on the arrays. The data obtained will be normalized using methods applicable to the performed experiment and we will perform a quality assessment of the data.

Upon completion of the miRNA profiling service, we will send you an email with a link to a secure web-server from which you may download the final report and all associated files. For further details on report content, please see overleaf.

**Getting Started**

Go to www.exiqon.com/services and fill in the request form. We will then contact you very shortly after you submit your request to further discuss your requirements. After we have agreed on the best way to proceed with the experiments, we will provide you with a free, no obligation quote.
At a glance
- Preserve your precious RNA samples
- Superior to DNA probes
- Get results in a few hours
- Detect miRNA in as little as 2.5 μg total RNA

Improved Northern Blot Detection of microRNAs
Exiqons miRCURY™ LNA technology enables sensitive and specific detection of miRNAs by Northern blotting. miRCURY™ LNA microRNA Northern blotting probes have high binding affinity and discrimination, enabling the specific and sensitive detection of miRNAs. Due to the high binding affinity of the miRCURY™ LNA microRNA Detection probes less than 1/10 the amount of sample is needed compared to traditional probes. Furthermore, the exposure time is reduced to just a few hours.

For researchers who wish to detect miRNAs on Northern blots by non-radioactive methods, we recommend the use of DIG-tailing, where multiple DIG moieties are added to the miRCURY™ probe.

Northern blot showing high specificity using miRCURY™ LNA Detection probes. The probe specificity was assessed using 32P-labeled perfect match, double mismatch and three single mismatch miRCURY™ LNA microRNA Detection probes in the detection of miR171 in A. thaliana flowers (1) and leaves (2). The filters were washed at low stringency and high stringency.

From Válóczi et al. 2004, Nucleic Acids Res. e175; reprinted by permission of Oxford University Press.

Product Description
Pre-designed miRCURY™ LNA microRNA Northern blot detection probes for are available for all known miRNAs in invertebrates, vertebrates and plants, as annotated in the miRNA Registry (miRBase) at The Welcome Trust Sanger Institute.

Custom miRCURY™ LNA microRNA Detection probes are available for your own miRNAs and other small RNAs.

Using miRCURY™ LNA microRNA Detection probes double and even single mismatches are readily discriminated as shown left.
miRCURY™ LNA microRNA Detection: in situ hybridisation probes

See precisely where your miRNA is expressed with a sensitivity and specificity not possible with probes.

At a glance
- Detect low abundance miRNAs
- Probes available for all miRNAs
- Single- or dual-base discrimination
- Probes are ready to be labeled or pre-labeled with your preferred detection method, e.g. DIG, biotin, fluorescence
- Fully developed protocols

Truly Enabling Technology
Exiqons miRCURY™ microRNA technology enables sensitive and specific detection of mature miRNAs by in situ hybridisation. For the detection of miRNAs, the development of miRCURY™ LNA microRNA in situ Detection probes has been a truly ground-breaking, enabling technology.

miRCURY™ LNA microRNA in situ Detection probes have high binding affinity and discrimination, enabling the specific and sensitive detection of miRNAs. Specific in situ detection of miRNA is possible in whole mounts, thin sections, single cells, frozen samples and in formalin-fixed, paraffin-embedded tissue sections (including archived samples).

miRCURY™ LNA microRNA Detection probes for the in situ detection of miRNAs have been used successfully in both animal and plant species. Their importance has been demonstrated in a number of publications, due to the expression patterns of miRNAs, which show highly specific tissue- and cell expression patterns. These probes have truly helped answer the questions of “when” and “where” a particular miRNA is expressed.

Detection of the brain specific miRNA-138 (red) in the hippocampus of mouse cells using miRCURY™ LNA microRNA Detection probes. DNA is labeled with DAPI (in blue).
The image was kindly provided by Dr. Javier Martinez, IMBA - Institute of Molecular Biotechnology, Vienna, Austria.

Specific detection of miR-122a (top), miR-206 (middle) and miR-124a (bottom) using miRCURY™ LNA microRNA Detection probes in in situ hybridisation of whole mount zebrafish embryos.
The images were kindly provided by Dr. Ronald Plasterk, Hubrecht Laboratory, The Netherlands.
miRCURY™ LNA microRNA in situ Detection probes in research
A number of papers have been published using miRCURY™ LNA microRNA in situ Detection probes. Wienholds et al. elucidated the temporal and spatial expression patterns of 115 conserved miRNAs in zebrafish embryos. One important conclusion from this work is that the role of miRNAs is in the differentiation or maintenance of tissue identity. Sokol and Ambros used miRCURY™ LNA microRNA Detection probes to detect miR-1-1 and miR-1-2 expression in Drosophila muscle. Nelson et al. used miRCURY™ LNA microRNA Detection probes to study the expression patterns of miRNAs in archived human brain tissue samples. The in situ expression patterns were able to help refine the data obtained from a microarray. Most recently, Obernosterer et al., have demonstrated differential distribution patterns of mature and pre-mirs in mouse embryos.

Pre-designed miRCURY™ LNA microRNA Detection probes
These probes are available for in situ hybridisation and northern blotting are available for all known microRNAs as registered and annotated in the miRNA Registry at The Wellcome Trust Sanger Institute. Control probes are also available.

Custom miRCURY™ LNA microRNA Detection probes
For in situ hybridisation and northern blotting are available for all other microRNAs, including pre-mirs, please inquire. The miRCURY™ LNA microRNA Detection probes are available in a “ready to label” format (using enzymatic labeling kits) and in a pre-labeled format e.g. labeled with DIG, biotin etc.

Control miRCURY™ LNA microRNA Detection probes
are available. Please go to www.exiqon.com

Ordering:
Go to www.exiqon.com/shop. Select your miRCURY™ LNA microRNA Detection product by Product Number, name of microRNA (must be entered exactly as given in the Sanger miRNA registry, e.g. “hsa-mir-1”) or sequence. For example, ordering a miRCURY™ LNA Detection probe for hsa-mir-1 can begin by entering 18008-00, hsa-miR-1 or UGGAAUGUAAAGAAGUAUGUA into the search window.

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<tbody>
<tr>
<td>XXXXXX-00</td>
<td>miRCURY™ LNA microRNA Detection probe, 250 pmol</td>
<td>ready to label*</td>
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"*Ready to label* means that the miRCURY™ LNA microRNA Detection probe can be enzymatically labeled with the detection moiety of choice, for example DIG, radiolabel, biotin or fluorophores.
General Conditions for Sale and Supply of Goods from Exiqon A/S.

The General Conditions shall apply, unless otherwise agreed in writing by both parties. In case of discrepancy between the parties on agreed conditions, the General Conditions given below shall apply.

1. Price, Quotation.
1.1 All orders are received to Exiqon’s acceptance and order confirmation in writing. An order is accepted at the price quoted at the date of the quotation. Quotations are valid for a period of 30 days only and fixed prices as specified in Exiqon’s Product Catalogue current at date of order are guaranteed except where changes in costs, rate of currencies, taxes, or the like may necessitate a price increase.
1.2 Unless expressly stated otherwise all prices are exclusive of V.A.T. or similar sales taxes.
1.3 Orders below 350 EURO will be charged a handling fee of 30 EURO.

2. Product Information, Drawings and Descriptions.
2.1 All information and data contained in product brochures and price lists are binding only to the extent that they are by references expressly included in Exiqon’s acceptance of an order.
2.2 All drawings and technical documents relating to the Goods or its manufacture submitted by one party to the other shall remain the property of the submitting party.

3. Delivery - Passing of Risk.
3.1 If no trade terms is specifically agreed delivery shall be Free Carrier (FCA, Vedbaek) (Incoterms 2000). The risk for accidental damage to the Goods will pass to the purchaser upon delivery to the purchaser or third party e.g. a carrier.
3.2 If the purchaser fails to accept delivery the purchaser shall be charged with the expenses incurred by Exiqon.
3.3 Exiqon will use its best efforts to deliver the Goods within the time agreed and if no time is agreed within a reasonable time but in no circumstances will Exiqon be liable for loss or damage of any kind caused directly or indirectly by any delay in delivery of the Goods.
3.4 Exiqon may make delivery by installments.

4. Payment.
4.1 Where no account has been agreed by Exiqon the Goods will not be delivered until Exiqon is paid the amount shown on the proforma invoice relating to the Goods.
4.2 Where an account has been agreed the price will become payable upon delivery and payment will be made by the Buyer within 30 days of the date on the invoice.
4.3 The Goods shall remain the property of Exiqon until payment has been made in full. If purchaser does not pay within the time stipulated Exiqon is entitled to charge interests on overdue payments at the rate of 2 (two) per cent per month.

5. Warranty.
5.1 Exiqon will repair or at its option replace any Goods manufactured by Exiqon which are proved to the reasonable satisfaction of Exiqon to be defective in material or workmanship provided such defects are notified to the seller within 12 (twelve) months of the date of despatch.
5.2 No warranty shall be undertaken for damage which is attributable to the following: Unsuitable or improper use, faulty assembly or commissioning by purchaser or third parties, fault or negligent handling, unsuitable utilities, chemical, electronically or electrical influences provided that they are not attributable to the fault of Exiqon.
5.3 Purchaser waives all rights to be indemnified for any consequential damages, e.g. loss of profit, lost suffered by third parties, and claim for damages which is not incurred on the goods themselves, unless it is established that such loss is due to gross negligence on Exiqon’s part or other parts for whom Exiqon is liable. If Exiqon should be liable compensation for defects is limited to 10 (ten) per cent of the net selling price.

6. Cancellation.
6.1 The purchaser is not entitled to cancel, extend or delay the contract or part thereof.
6.2 If Exiqon consents to the purchaser cancelling the contract or part thereof and returning any Goods, the purchaser shall be liable to pay Exiqon current handling charges.

7. Product Liability.
7.1 Exiqon is not liable for damages to real property or movables unless it is established that such damage to real property or movables is due to gross negligence on Exiqon’s part or others for whom Exiqon is liable.
7.2 Exiqon is under no circumstances liable for personal injury or damages if such personal injury or damages are due to the use of the delivered products contrary to Exiqon’s manuals or technical specifications or due to negligent acts on the part of others than Exiqon, i.e. subsuppliers or independent transporters.
7.3 Exiqon is under no circumstances liable for indirect loss, loss of profits, or any other kind of consequential loss.
7.4 Exiqon is liable for personal injuries and for damages to real property or movables intended for noncommercial purposes according to the rules in the Danish Act of Product Liability to the extent that Exiqon’s liability is not limited pursuant to clause 7.1 through 7.3.
7.5 In the event that Exiqon is held liable according to the rules concerning “product liability” in relation to a third party, purchaser is obliged to indemnify Exiqon from all claims to the extend that Exiqon has limited its liabilities according to clause 7.1 through 7.4. If a third party should claim damages from one of the contracting parties in respect to the delivery made under these General Conditions, this party is obliged to inform the other party with the outmost dispatch.

8.1 Any delay or failure of performance of either party shall be considered as cases of relief of responsibility to the extent that such delay in or failure of performance are caused by occurrences after the acceptance of the quotation and are beyond the control of the party affected including but not limited to: Industrial disputes, fire, war, general mobilisation of unforeseen military mobilisations, requisition, general shortage of materials, shortage of transport, civil commotion, import bans or export bans, restrictions in the use of power, defects on production facilities or delays in deliveries by subsuppliers.

9. Disputes and Applicable Law.
9.1 Any disputes arising out of the contract regarding the interpretation and application of the contract shall be governed by Danish Law.
9.2 The venue for any legal actions instituted by purchaser against Exiqon shall be The Maritime and Commercial Court in Copenhagen.
9.3 Legal actions against purchaser can be instituted at Exiqon’s discretion at The Maritime and Commercial Court in Copenhagen or at purchasers normal venue.

Latest revision: February, 2004
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