



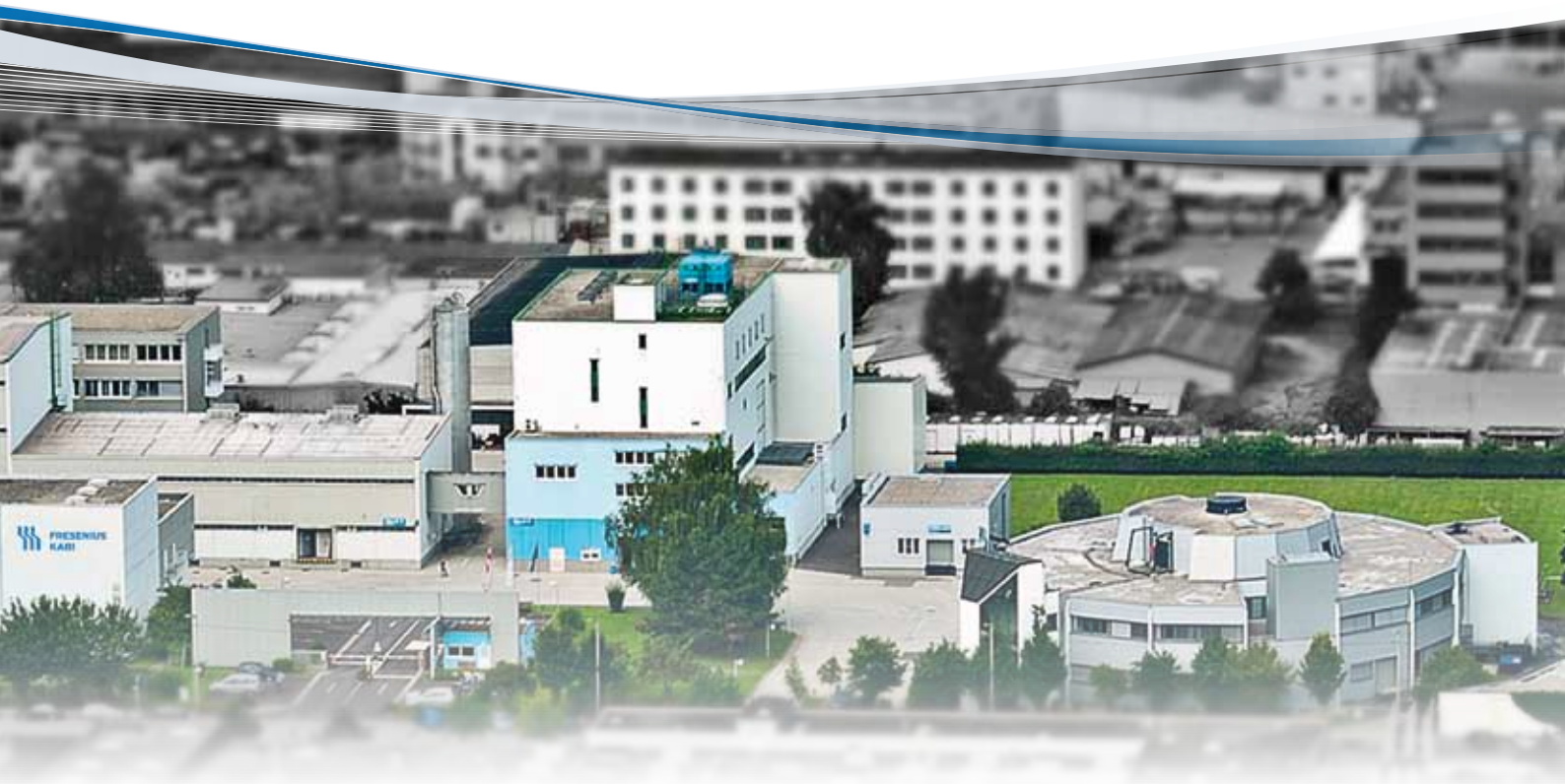


## WORLDWIDE

### >> local and global

The Fresenius Kabi location in Linz, Austria has a long record in development and manufacturing of medicinal carbohydrate products. It is one of the two plants of Fresenius Kabi Austria GmbH; the other is in Graz and specializes in infusions. The company is a subsidiary of Fresenius Kabi AG, which is the market leader in infusion therapy and clinical nutrition in Europe and holds leading positions in important countries of Latin America and the Asia-Pacific region. Within I.V. generic drugs, Fresenius Kabi counts among the leading suppliers in the US market.

Fresenius Kabi produces not only finished infusion products but also the related containers and delivery devices. Several of its plants have special competence in producing active ingredients; Linz is one of these. Fresenius Kabi AG in turn is a division of the global health care group Fresenius SE.



## HISTORY OF SUCCESS

### >> long-standing expertise

The history of the business in Linz began with Laevosan GmbH, founded in 1947 by a group of carbohydrate scientists. Its early products included pharmaceutical-grade fructose (laevulose - hence the company name) and inulin. Continuing research and development led to what are now the site's two major products: hydroxyethyl starch (HES) and lactulose. The company developed and patented the production processes for both of these products.

Laevosan GmbH was acquired by the Fresenius concern in 1997. It was merged with the former Leopold Pharma GmbH of Graz, which was already part of the Fresenius group, to form Fresenius Kabi Austria GmbH. These mergers brought the company two new centers of excellence in key technologies. And they linked these established companies into an international network of other operations with complementary technical expertise and a worldwide presence. Today, Fresenius Kabi AG has an impressive portfolio of established, market-leading products, and a formidable spectrum of research and development capabilities.

## IN THE HEART OF EUROPE

### >> thriving center

On the banks of the Danube, Linz is the capital of Upper Austria and a vibrant business center. It has about 200,000 inhabitants and is part of a conurbation with roughly twice this population.

Close to both Germany and the Czech Republic, the region has long been a manufacturing heartland. Traditionally a city of steel and chemical industries, Linz has successfully diversified into high-tech sectors and has also blossomed as a centre of culture and the arts. Its universities and proximity to other academic locations mean there is no shortage of qualified people.







## LACTULOSE

### >> a gentle laxative

Chronic constipation quite often needs to be treated with a laxative. Lactulose is a sugar that is not digested or absorbed in the small intestine, so it reaches the lower part of the gut intact. There, Bifidobacteria and Lactobacilli can use it as an energy source, which stimulates their growth. The bacteria metabolize lactulose to acidic products. The increase in acidity draws more water into the colon, making the stool softer, and also gently activates peristalsis. The combination of prebiotic, osmotic and activating effects makes lactulose an effective laxative. It is well tolerated in long-term use, even in patient groups regarded as sensitive, and has been in regular use since the 1960s.

### >> eliminating ammonia

At higher doses, lactulose also promotes excretion of ammonia. This effect makes lactulose the treatment of choice for portal systemic encephalopathy (PSE), a complication of liver cirrhosis caused by elevated blood ammonia.

### >> natural potential

Chemically, lactulose is an isomer of the natural milk sugar lactose, and is produced from lactose. With its excellent safety profile, it is also suitable for use as a prebiotic food ingredient, and another promising new market is the animal feed industry.

### >> top supplier

Fresenius Kabi Austria is one of the world's major lactulose suppliers. The production process was developed in Linz and is patented. We manufacture lactulose in two plants: one in Linz, Austria, and one in Vicchio del Mugello, Italy (SCM).

In Linz we make liquid lactulose (67% w/v) that can be supplied either in bulk or in a range of filled and packaged presentation forms. The SCM plant in Vicchio also produces liquid lactulose (up to 70% w/v) and is a leading producer in Europe of highest-purity, crystalline lactulose API according to the EP specification, with a production process also approved by the FDA. The liquid lactulose API from both plants meets the requirements of European and US pharmacopeias (EP, USP); the lactulose liquid from the SCM plant also satisfies JP.

### >> formats

Lactulose is supplied in unflavored form and in several different flavors in a wide range of container formats:

API containers for lactulose liquid:

- 1250 kg IBC (standard)
- 250 kg drums
- 25 tonnes tank container

API containers for lactulose crystals:

- 50 kg drums

Finished product presentations:

- PET or HDPE bottles in various sizes up to 1000ml
- Single dose sachets in boxes of up to 100 single doses (lactulose liquid and crystals)





## HYDROXYETHYL STARCH

### >> quick fix

A large loss of blood volume, hypovolemia, can happen for a variety of reasons, for example bleeding, severe vomiting, dehydration or severe burns. Since hypovolemic shock can quickly become life threatening, it is important to replace the lost blood volume as quickly as possible so that the patient's circulation keeps functioning. This is often done with colloidal infusions, and hydroxyethyl starch (HES) is one of the most proven and trusted colloidal substances used in this group of plasma expanders.

HES solutions are well tolerated and safe and have good rheological properties. In the best formulations, HES does not accumulate in the plasma, is excreted at a predictable rate, and has a minimal effect on blood coagulation.

### >> stabilizer

HES is also used as an ingredient of cryoprotectant solutions for preserving frozen cells and tissues. A new application of HES that is in development is the Hesylation® technology, which shows considerable promise as a way of modifying drug targeting and kinetics.



### >> waxy corn

Chemically, HES is derived from waxy corn starch, which is obtained from special maize varieties that produce nearly exclusively amylopectin. The raw material is first modified by hydroxyethylation, and then hydrolyzed to reduce the average molecular weight. The molecular weight influences the rate of elimination in vivo.

With the degree of hydroxyethylation, which protects against rapid breakdown by amylase enzymes, we can control the rate of degradation of the starch. A very important aspect for HES performance is to achieve as narrow a molecular weight range as possible. As one of the most experienced manufacturers, Fresenius Kabi has this issue well under control. After purification and drying, HES is packed immediately.

### >> formats

HES powder is supplied in 25kg bags and Bigbags. With an annual production output of several hundred tonnes of HES, Fresenius Kabi's plant in Linz is among the world's largest producers of this active pharmaceutical ingredient. The production process is approved by the FDA.





## SINISTRIN

### >> renal diagnosis

An important measure of kidney function is the glomerular filtration rate (GFR). To measure this parameter, a marker substance is injected into the blood stream, and its rate of excretion in the urine is compared to the plasma concentration. The marker substance needs to be non-toxic, not endogenous in the circulation, neither reabsorbed nor secreted in the kidney, and measurable. Sinistrin meets all of these requirements. It is often preferred to the alternative, inulin, because it is much more soluble in water and easier to handle.

### >> red squill

Like inulin, sinistrin is a naturally occurring sugar polymer of the fructan group. It is obtained from the bulb of red squill (*Urginea maritima*) in a gentle extraction process. Undesired extracts, impurities and colored compounds are removed in a series of purification steps. The solution is carefully concentrated and dried under controlled conditions to yield the solid product.



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### >> formats

Sinistrin is supplied as a finished product in 20ml ampoules, each containing 5000 mg Sinistrin for injection. The ampoules are available in a 5x5 bundle package under a well-known Fresenius Kabi brand name.







## AT YOUR SERVICE

### >> all-round customer support

Supplying APIs and finished products to our customers all over the world is an important part of our business. We offer lactulose and HES as bulk APIs and a contract manufacturing service for lactulose in finished product form, to be marketed under our customer's brands. Fresenius Kabi Austria's own successful lactulose brand Laevolac® is registered and marketed in numerous countries around the world.

We pride ourselves on providing our industry customers with the backup they need. All the know-how of our expert teams is available to make these projects a success.

The services we offer include

- Advice on choosing container formats
- Wide range of containers
- Compiling and supplying regulatory documentation such as drug master files (USDMF, ASMF, CEP), common technical document (e-CTD) dossiers
- Competence in regulatory issues
- Marketing consulting
- Logistics & distribution concepts

Partnerships with customers are backed up by regular visits by our sales team. On the following pages, you can find more details about some of our specific areas of competence in the Linz plant.

### >> product partnering

The business-to-business platform Fresenius Kabi Product Partnering is dedicated to contract manufacturing, offering our partners easy access to Fresenius Kabi's advanced development and manufacturing capabilities for sterile pharmaceuticals and sterile medical devices ([www.fresenius-productpartnering.com](http://www.fresenius-productpartnering.com)).





## PROGRESS AT WORK

### >> production plant

The plant in Linz manufactures the APIs lactulose, hydroxyethyl starch (HES), and sinistrin. The plant runs around the clock, seven days a week. It also houses a filling and packaging section to process the API lactulose into ready-to-use finished products. Dedicated filling lines side by side with the lactulose API production ensure that the finished lactulose products are made seamlessly after bulk production. Flexibility and continuing innovation guarantee the excellent shipping quality of our finished products. Third party packaging activities also include the filling and packaging of vials, bottles, and blister packs.

### >> process development

Our highly efficient, environmentally friendly processes are the work of our excellent process development department. Besides continuous improvement of existing processes, the team works on the development of new products, from pilot scale to full scale.

The department is regarded as the carbohydrate competence center within the Fresenius Kabi group. An area of special technological competence is the use of membrane separation technology. We have successfully patented several aspects of our processes and have ongoing research partnerships with universities.



### >> logistics & distribution

Order-related and just-in-time logistics ensure reliable delivery and the maximum possible shelf life of the products for all our customers outside and inside the Fresenius Kabi group. Our highly motivated and competent service team coordinates the worldwide distribution of our products, helping you to deliver value across the whole supply chain.



## INTEGRATED MANAGEMENT SYSTEM

The integrated management system for quality, risk, safety, health and environment is the key to Fresenius Kabi's major goal: reliable quality - for our customers, and for patients all over the world.

### >> quality unit

Fresenius Kabi Austria takes quality control very seriously. Our quality unit tests all incoming starting materials, does in-process control and finally analyzes bulk and finished products for compliance with the specifications. The unit is also responsible for microbiological and hygiene monitoring and for vendor qualification.

Our analytical capabilities are tailored to the plant's focus on carbohydrate products, and also include GPC, HPLC and GC. Quality tasks and data are handled with an up-to-date and cGMP-compatible laboratory information system.



### >> fully audited

Plant, products, processes and procedures are continuously monitored and reviewed by our quality assurance unit to ensure they comply with specifications.


Specifications and procedures are kept up to date with EU GMP and US cGMP regulations. Compliance with those regulations is audited by regulatory authorities, including the US FDA, and also by customers.

### >> environment

Responsible interaction with the environment is an important part of Fresenius Kabi's business philosophy. All the products of the Linz plant are derived from natural, renewable sources such as lactose and maize starch. In all our process development activities, we consider how to minimize the environmental impact. Continuous surveillance of all material flows and cycles allow enlightened and economical deployment of resources.

### >> safety and health

Our mission "caring for life" means we also look after the health and well-being of our employees. The very high levels of reliability and quality we demand can only be achieved when the people involved are enabled to do their best work. And so both our safety programs and the medical care offered to our employees are well above average.





**FRESENIUS  
KABI**

caring for life

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