1. The molecule

Spiramycin consists of 3 varieties: Type 1, 2 und 3. It depends on the residual at the lactone-circle.

![Spiramycin molecule diagram](image)

**Figure 1: Spiramycin 1 - 3**

Spiramycin has the following composition in a dry state:

- Spiramycin I: at least 80,0 %
- Spiramycin II: at the most 5,0 %
- Spiramycin III: at the most 10,0 %

These molecules are sold for humans in Germany, Austria and Swiss with the name **Rovamycin** or **Selectomycin**. In the veterinary medicine, the name of these preparations is Spiramastin and Suanovil 20, which are just available in Austria.
2. Macrolides

Relevance of macrolides in medicine

Macrolides are a group of antibiotics which is characterized by a specific mechanism of action. They all act bacteriostatic and depending on the substance and its concentration they can act as bactericides, too.

Among spiramycin there are several different other partly half-synthetic macrolides, such as erythromycin A, clarithromycin, azithromycin and roxithromycin.

![Figure 2: Erythromycin A](image)
![Figure 3: Azithromycin](image)

Just as spiramycin, erythromycin A, azithromycin and all other macrolides consist of a lactone-circle and different attached sugar molecules.

In practice it is especially used, when other antibiotics do not work anymore or the patient has a penicillin allergy.

Specifically spiramycin is deployed against inflammations of gingiva, oral mucosa, nasal-pharyngal-space, tonsils, paranasal sinuses, tympanum, lung and skin. It is even used for prevention of inflammations during interventions in the oral area.

However the main application of spiramycin is the treatment of toxoplasmosis caused by a parasitic pathogen, which can be dangerous during pregnancy.

The range of applications seems very broad on paper, nevertheless spiramycin is rarely used in relation to its abilities.

An important reason for this is that there are many new macrolides with the same but improved effect such as a more reliability, less side effects and a better bioavailability.
3. The mechanism of action

Unlike Penicilline, that directly kills the bacteria-membrane and works therefore bactericidal, spiramycin has a growth-inhibiting effect and acts primarily bacteriostatic. It is especially working against bacteria with an active metabolism. Inactive bacteria are merely adequately affected. The range of the pathogens for spiramycin and most of the macrolides are gram-positive cocci, rod cells and gram-negative cocci.¹

![Translation Diagram](http://flexikon.doccheck.com/de/Makrolidantibiotikum)

2. Elongation

Figure 4: ribosome on the mRNA

The inhibition of growth means the embargo of the protein biosynthesis (translation), hence the translation from the base-sequences to the amino-acid-sequences. This occurs at the ribosomes of the bacterial prokaryotes, where the molecule binds for inhibition.²

At the beginning of the protein biosynthesis the ribosome is composed of two subunits, one small subunit, which is responsible for the translation of the genetic code, and one big subunit, which the amino acids connect to. At this spot (Peptidyl-Transferase-Center) spiramycin is preventing the further translation of the polypeptides, whilst locking a translocase enzyme. This enzyme is the elongation factor G that is overlayed by the sugars of spiramycin, which results in the inhibition of the migration and growing of one polypeptide chain.³⁴

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¹ [http://flexikon.doccheck.com/de/Makrolidantibiotikum](http://flexikon.doccheck.com/de/Makrolidantibiotikum)
² [http://www.biokurs.de/skripten/bilder/translelo.jpg](http://www.biokurs.de/skripten/bilder/translelo.jpg)
³ [http://www.laborpraxis.vogel.de/wissenschaft-forschung/articles/120007/](http://www.laborpraxis.vogel.de/wissenschaft-forschung/articles/120007/)
⁴ [http://flexikon.doccheck.com/de/Spiramycin](http://flexikon.doccheck.com/de/Spiramycin)
One disadvantage of spiramycin is the low bioavailability. The absorption of spiramycin is incomplete with an oral bioavailability of 33% to 39% (range, 10% to 69%). The rate of absorption is slower compared to erythromycin and is thought to be due to the high pKa (7.9) of spiramycin, suggesting a high degree of ionization in the acidic stomach.\(^5\)

The greatest disadvantage of the mechanism of action is the developing resistance, which occurs quite easily because the bacteria only have to modify their ribosomal enzyme system. Moreover, macrolides carry the problem of cross-resistance: If one bacteria becomes resistant to one macrolide, it is resistant to every other macrolide, too. Hence, spiramycin is like mentioned before an outdated medication.\(^6\)

### 4. The synthesis in Streptomyces

**Streptomyces**

Streptomyces are a type of bacteria, which grow mainly in forest soils. There they are responsible for the typical forest smell, which is referred to Geosmin. Streptomyces produces some antibiotics, which are encoded in the arms of the genome. The antibiotics are part of the secondary-metabolism. The primary metabolism is in the middle of the genome - in the so called core. Streptomyces produce the antibiotics quite fast, once they are under pressure.

**Gene-Cluster and the enzymes**

The genetic information of Spiramycin contains 45 genes. The 5 biggest are srmGI to srmGV, which encode the main part of the polyketide-synthase (PKS). At the same

\(^5\) [https://www.drugs.com/mmx/spiramycin.html](https://www.drugs.com/mmx/spiramycin.html)

\(^6\) [http://flexikon.doccheck.com/de/Makrolidantibiotikum](http://flexikon.doccheck.com/de/Makrolidantibiotikum)
time genes with a Spiramycin-resistance, some transportproteins and enzymes for the hybridization of the sugar-molecules, are necessary.\(^7\)

Figure 6: anabolism of polyketides

The PKS is the most important part of the Spiramycin-production. It belongs to the Type-I-PKS, that is why it is big and has four active sites. The four active sites are responsible for the growth of the polyketide. The construction of the polyketide is similar to the anabolism of fatty acids. One methoxymalonyl-CoA is fixed to the substrate via a claisen-condensation. Spiramycin belongs to the reduced polyketides, which means that the double bonds are reduced to saturated compounds\(^8\)

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\(^7\) Organization of the biosynthetic gene cluster for the macrolide antibiotic spiramycin in Streptomyces ambofaciens; Fatma Karray and others; Microbiology, August 2007

\(^8\) Naturstoff-Lego; Uschi Sundermann, Susanna Kushnir, Frank Schulz; Nachrichten aus der Chemie | 59 | Januar 2011 | [www.gdch.de/nachrichten](http://www.gdch.de/nachrichten)