Pharmacology and Nutrition (HNH 23306) October-November 2021

- Personal Leaflet Document -

General points
Use this file as a template to build your own 'leaflet' document. Points for consideration and clarification are written in Italics

- *You will be working on this file individually; groups will be formed after you've handed in this document.*
- *Copy this file from Blackboard and store it using a new file name as follows: <family name_first name_ drug name*_tutor name> *may be abbreviated, use at least 6 characters*
  Example : rutte_mark_amoxic_paulien.doc

- *Also type your given name and family name **HERE :** Rivaroxaban, Lisanne de Jonge*

- *Upload the file to Brightspace before Wednesday November 20th (0.00h).*
- *Think already about possible exam questions (two to be provided by each group of 6 students)*
- *Please be concise and clear in your answers and descriptions. The total (including this front page and text already present) document should not be longer than 6 pages (Font Calabri 11pt, line space 1)*
- *And remember : **NO copy and paste ! USE YOUR OWN WORDS AND SHOW YOU UNDERSTAND THE MATTER..***

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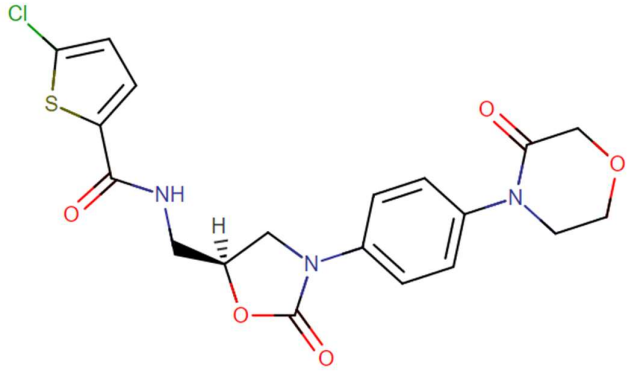
Drug name and chemical form

Rivaroxaban is not a salt and belongs to the base. Its chemical formula is $C_{19}H_{18}ClN_3O_5S$. It is an antithrombotic agent, making it a direct factor Xa inhibitor. The ATC code is B01AF01.



Formulation

Rivaroxaban is given in a film-coated tablet. The tablets are light yellow, round biconvex with a 6 mm diameter, 9 mm radius of curvature and they are noticeable by their BAYER-cross on one side and "2.5" and a triangle on the other side. Due to the coating of the tablet, the pH in the stomach does not release the rivaroxaban there. This way the rivaroxaban can slowly come into the blood via the liver or kidneys. One tablet contains 2.5mg rivaroxaban. The tablet should be used oral. The tablet should be taken twice a day. The rivaroxaban is fast absorbed and reaches its best absorption point in 2-4 hours. At the end two-thirds of the dose is metabolized to the blood. The half-life of rivaroxaban is 5-9 hours in adults and for elderly 11-13 hours.

Mechanism of action and pharmacological group

Rivaroxaban enters the body orally, which gives it its oral bioavailability. Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms which gives it the path to the blood. It is a very selective direct factor Xa inhibitor. By its inhibition of factor Xa, rivaroxaban disturbs the intrinsic and extrinsic blood flow of the coagulation cascade. By this interruption rivaroxaban makes sure the thrombin formation and development of thrombi does not occur, this is the intended clinical end-effect.

The protein binding of rivaroxaban with CYP3A4, CYP2J2 and CYP-independent mechanisms is about 92% to 95% complete. The process takes place in the liver and/or in the kidneys.

Indication(s) for use

Rivaroxaban should be taken twice a day. With or without the consumption of food. The tablet should be swallowed, but if not possible it could be crushed and mixed with water and administered directly orally.

When rivaroxaban has entered the blood, it makes sure factor Xa is not taking the lead in the blood. By doing this rivaroxaban as inhibitor makes sure the blood stays in the good consistency and does not clod, as will be the other case when rivaroxaban is not presented.

This way rivaroxaban makes sure his user does not get blood clotting in the arteries and thus get Thrombin (Mnemonic for Nursing, 2021).
Factor Xa in the presence of Ca^{2+}, phospholipid and factor Va starts the process of prothrombin into thrombin, which is the main enzyme of the cascade. When not stopped by rivaroxaban this factor Xa would make the cascade go on and on which will result in solidified blood within minutes. Rivaroxaban thus makes sure the cascade slows down or stops on time.
Other drugs that could help solve the problem are Apixaban. This drug has the same working as rivaroxaban (Mnemonic for Nursing, 2021). Or the drug Heparin, which is a co-factor for antithrombin III, one of the most important inhibitors for this (Rigan, S., 2020).

Source;
Mnemonic for Nursing Pharmacology (NCLEX). Factor Xa Inhibitors (Rivaroxaban). (2021, November 10). [Video]. YouTube. https://www.youtube.com/watch?v=Eb4EjSZlRs4

Rigan, S. (2020, October 28). RANG & DALE'S Pharmacology 9th edition (TRUE PDF). https://www.academia.edu/44387934/RANG_and_DALES_Pharmacology_9th_edition_TRUE_PDF_

Contra-indications and (or) precautions

When a potential user has a lesion or condition, it is not advised or should first be discussed with a medical professional. As rivaroxaban makes sure the blood does not clod, it can cause a bleeding of a wound to keep going instead of clotting when the Prothrombin would be active. This bleeding could arise inside the body as well as outside the body resulting in when not stopped, a death of the person.
Elderly people often need rivaroxaban more than young adults as the blood clotting in small vein like the of elderly could result in for example an infarction in the brain, because of the blood clots there is no moving space for the 'normal' blood to move like the blood circulations wants it. But elderly should be carefully as their risk of excessive bleeding could be bigger by every age.
When someone has a high risk on Haemorrhagic it is risky to take rivaroxaban. As Haemorrhagic means that the vessel somewhere inside the body is ruptured and the blood is going into other parts of the body. Meaning people with a high risk for Haemorrhagic can not or not easily stop this bleeding by themselves (their body cells).

Pharmacokinetic (PK) properties of the compound

- About the oral availability. The rivaroxaban is fast absorbed and reaches its best absorption point in 2-4 hours. At the end two-thirds of the dose is metabolized to the blood.
- By the coated tablet the rivaroxaban reaches the blood before it is demolished by the pH of the stomach. Therefore, the rivaroxaban is covered in a coating.
- The half-life of rivaroxaban is 5-9 hours in adults and for elderly 11-13 hours.
- By metabolising, the rivaroxaban is easily connected with the CYP3A4, CYP2J2 and CYP-independent protein mechanism and can reach the blood and can start inhibiting factor Xa.

- The major route of excretion of rivaroxaban is via the urine. Two-thirds is excreted in urine and the rest in feces.
- The steady state Vd of rivaroxaban in the body is 50L, this is the volume of distribution of rivaroxaban.
- The dose of the rivaroxaban should be taken twice a day. Vd is 50L, to keep (some) of this in the blood the tablet should be taken just before the steady states ends as from this point there is no working rivaroxaban in the blood. In conclusion if you look at the half-life of 5-9 hours for adults you can conclude that the tablet should be taken twice a day. As a day exist out of 24 hours, taking 2 per day gives 12 hours of time that the drug should be working. The half-time point is earlier reached than the steady state, so the steady state will than be around 12 hours. Getting the rivaroxaban from the second tablet into the blood takes some time as well, which eventually gives the time for the first tablet to be metabolized and for the second pill to start at that time with the metabolization. To ensure a constant rivaroxaban in the blood.

Potential side-effects

A side-effect could be excessive bleeding. Someone whose blood is very thin by the rivaroxaban taken and starts bleeding by accident of a cut in the hand for example, has the side-effect that the bleeding will not stop or will be very excessively. Without actions like mechanical compression the bleeding will not stop by the body itself. As the mechanism of blood clotting is not fast enough due to the drug.
A second side-effect could be with an artery bypass graft surgery. Without knowing the patient is taking the rivaroxaban the surgent will cut in the body and in the artery's which will bleed excessively and will not stop doing this without help from outside the body.
People with renal impairment could bleed excessively. As the renal impairment makes the liver not work properly, this way their comes more rivaroxaban in the blood as the liver cannot filter this, which makes the person more at risk to get excessive bleeding when getting a wound or something similar.

Possible interactions with other drugs

When rivaroxaban is combined with ketoconazole (400mg a day) or ritonavir (600mg twice a day) leads to an increase in mean rivaroxaban C_{max} by 2.6/2.5 times. Or with the drug AUC this leads to a 1.7/1.6 times higher concentration of rivaroxaban in the blood. The concentration of rivaroxaban in the blood goes up because those drugs are inhibitors of CYP3A4 and P-gp, this gives the rivaroxaban the opportunity to bind with the CYP3A4 and P-gp to get to the blood. By more concentration of rivaroxaban in the blood, the change of bleeding excessively when a vein or a wound goes open is much higher. Something you want to prevent from happening.
Another two drugs are also not advised to take with rivaroxaban. Those are NSAIDs and platelet aggregation inhibitors, as they have a same effect as rivaroxaban, which is letting the blood not clod. Taking those drugs together gives the blood no change to clod, which results in excessively bleeding during accidents.
The strong CYP3A4 inducer rifampicin is not helpful to take with rivaroxaban. As this inducer leads to an approximately 50% decrease in mean rivaroxaban in the blood. Taking this inducer works against the effect of rivaroxaban. This way the user can get blood clotting again. Resulting in a heart attack for example.

Possible interactions with food

Rivaroxaban should be taken oral. The rivaroxaban absorption is fast and almost complete. The oral availability of rivaroxaban is 80-100% which is quite high per 2.5mg and 10mg dose. Taking rivaroxaban with or without food does not affect the purpose of rivaroxaban. For example, when a user can't swallow the tablet, it could be crushed dropped into water or dropped into apple puree and immediately consumed.

Dose adjustments for special groups/patients

People with a renal impairment, an impairment when the kidneys stopped working and cannot remove waste and extra water from the blood or keep body chemicals in balance. Do not have to adjust the dose of rivaroxaban and are able to take rivaroxaban.
Young patients have less high plasma concentration then elderly patients. This comes down to approximately 1.5 times higher, which comes due to reduced total and renal clearance. To conclude elderly do not have to adjust the dose of rivaroxaban. But should be careful just because the risk of excessive bleeding becomes higher by increasing the age.
For children rivaroxaban is not recommended as the safety and efficacy of the drug is not tested yet. There is no data available about the working of rivaroxaban under the age of 18 years old.