1.3.1	Bismuth subcitrate
SPC, Labeling and Package Leaflet	AT

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SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

1.3.1	Bismuth subcitrate
SPC, Labeling and Package Leaflet	AT

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<Invented name> 120 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 120 mg bismuth oxide (as tripotassium dicitratobismuthate (bismuth subcitrate)).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

White to almost white, round (diameter: 10 mm) film-coated tablets, slightly biconvex with bevelled edges.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of gastric and duodenal ulcers.
- Aid in *Helicobacter pylori* eradication in combination with other medications.
- Gastritis associated with dyspeptic disorder, when eradication of *Helicobacter pylori* is desired.

4.2 Posology and method of administration

Posology
The following treatment schemes are recommended:
- 1 tablet four times daily on an empty stomach (half an hour before main meals and before bedtime),

or
- 2 tablets two times daily on an empty stomach, half an hour before breakfast and half an hour before dinner or before bedtime.

The maximum duration of one course of treatment is 2 months. At least two months should elapse before a new course of treatment with bismuth containing products.

For the treatment of duodenal or gastric ulcers the duration of one course of treatment is 4 to 8 weeks.

For the eradication of *H. pylori* the selection of combination therapy and duration of treatment (7 to 14 days) should consider the individual patient's drug tolerance, and should be undertaken in accordance with regional resistance patterns and treatment guidelines.

Paediatric population
The use in children and adolescents is not recommended.

Method of administration
The tablets should be swallowed whole with a sufficient amount of water.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Severe renal impairment.

4.4 Special warnings and precautions for use

Prolonged use of high doses of bismuth compounds is not recommended because this has occasionally led to reversible encephalopathy. If <Invented name> is used as recommended, the probability of this is very small. However, concomitant use of other bismuth-containing compounds is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction

No other medicines, in particular antacids, food or drink, milk, fruit or fruit juices, should be consumed within half an hour before or after a dose of <Invented name> as they may influence its effect.

A decrease in the absorption of tetracyclines is theoretically possible when used concomitantly.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are insufficient data on the use of tripotassium dicitratobismuthate during pregnancy in humans to assess its potential harmful effects. To date, no indications of harmful effects have been found in animal tests.
Due to lack of data, use during pregnancy is not recommended.

Lactation
There are insufficient data on the use of dicitratobismuthate during lactation in humans to assess its potential harmful effects.

4.7 Effects on ability to drive and use machines

There are no known data on the effect of this product on the ability to drive. However, an effect on the ability to drive or operate machinery is unlikely.

4.8 Undesirable effects

System Organ Class	Very common (≥ 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Very rare (< 1/10,000)
Immune system disorders			anaphylactic reaction
Gastrointestinal disorders	blackening of the stool	nausea, vomiting, constipation, diarrhoea	
Skin and subcutaneous tissue disorders		rash, pruritus	

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system

listed in Appendix V.

4.9 Overdose

Symptoms
Acute, major overdose can lead to renal failure with a latency period up to 10 days.

Management
Single exposure to a very high dose should be treated with gastric lavage, followed by repeated administration of activated charcoal and osmotic laxatives. In general, this will prevent bismuth absorption to such extent that additional treatment should not be required.

Determination of bismuth concentrations in blood and urine is necessary both in the case of acute and potentially chronic intoxication, so that the symptoms can be attributed to increased bismuth exposure. If the symptoms are due to acute or chronic bismuth overdose, the administration of chelation therapy with dimercaptosuccinic acid (DMSA) or dimercaptopropane sulphonic acid (DMPS) should be considered. If there is also evidence of severe renal dysfunction, chelation should be followed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for acid related disorders, Other drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD), ATC code: A02BX05.

Mechanism of action
Under the effect of gastric acid, a precipitate is formed from tripotassium dicitrato bismuthate, which adheres primarily to the ulcerated area and inhibits the activity of pepsin. Tripotassium dicitrato bismuthate also protects the mucosa by stimulating the synthesis and secretion of endogenous prostaglandins, hence increasing bicarbonate and mucin production. In addition, tripotassium dicitrato bismuthate has antibacterial activity against *Helicobacter pylori*. Eradication of this bacteria is followed by an improvement in the histological picture and symptomatic improvement.

Pharmacodynamic effects
Tripotassium dicitrato bismuthate contributes to the healing of a high percentage of gastric and duodenal ulcers. Its antibacterial effect is associated with a lower frequency of ulcer recurrence in the first year after treatment discontinuation compared to some other agents.

5.2 Pharmacokinetic properties

Absorption
Tripotassium dicitrato bismuthate exerts a local action. However, small amounts of bismuth are absorbed (less than 0.2 % of the dose) during therapy.

Distribution
Bismuth is distributed mainly into the kidneys. Only trace amounts can be detected in other organs.

Biotransformation
Tripotassium dicitrato bismuthate precipitates locally in the stomach under the influence of gastric acid, forming insoluble compounds, possibly bismuth oxychloride and bismuth citrate.

Elimination
The vast majority of the ingested bismuth is excreted with faeces. Of the small amount that is absorbed, urinary clearance is approximately 50 mL/min. At least a 3-compartment model is needed to describe the excretion of bismuth over time. The half-life is 5-11 days.

5.3 Preclinical safety data

Oral single-dose of bismuth did not increase mortalities in rats at doses up to 2000 mg/kg. There were no significant changes attributed to treatment with bismuth on clinical signs, body weights, food consumption, haematology, clinical chemistry, urinalysis, organ weights, necropsy, or histopathological findings in the 28-day repeated oral dose toxicity study. The no-observed-adverse-effect level (NOAEL) of bismuth was determined to be 1000 mg/kg for males and females. No signs of hepatotoxicity were observed. There was also no presence of histopathological changes in the bone marrow or the lymphatic organs (thymus, spleen, lymph nodes).

The mutagenicity of bismuth cannot be assessed due to many shortcomings of the studies.

No definitive studies on the effects of bismuth citrate administration on male or female fertility and early embryonic development have been conducted. In rabbits maternal toxicity was apparent. However, no adverse effects upon pre- or post-implantation loss, numbers of viable foetuses or foetal development were observed. Tripoteassium dicitratobismuthate was not considered phototoxic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Maize starch
Povidone K30
Polacrillin potassium
Macrogol 6000
Magnesium stearate (E470b)

Film coating
Polyvinyl alcohol
Macrogol 4000
Talc
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package in order to protect from light and moisture.
This medicinal product does not require any special temperature storage conditions.

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6.5 Nature and contents of container

Blister (OPA/Alu/PVC foil, Alu foil): 28, 30, 40, 42, 45, 56 and 60 film-coated tablets, in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: [To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

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LABELLING

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PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX/for blisters

1. NAME OF THE MEDICINAL PRODUCT

<Invented name> 120 mg film-coated tablets
Bismuth oxide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 120 mg bismuth oxide (as tripotassium dicitratobismuthate (bismuth subcitrate)).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablet

28 film-coated tablets
30 film-coated tablets
40 film-coated tablets
42 film-coated tablets
45 film-coated tablets
56 film-coated tablets
60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

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9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

<Invented name> 120 mg

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MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

<Invented name> 120 mg film-coated tablets

Multilingual blister:
<Invented name> 120 mg tablets

Bismuth oxide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

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PACKAGE LEAFLET

Package leaflet: Information for the patient

<Invented name> 120 mg film-coated tablets
Bismuth oxide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What <Invented name> is and what it is used for

Upper abdominal symptoms may be caused by an inflammation of the lining of the stomach or duodenum (the first section of the small intestine). Sometimes an ulcer is also present. <Invented name> heals ulcers, and mucosal inflammation by forming a protecting layer (a kind of patch) and helps stop further irritation caused by stomach acid. It also has antibacterial activity against *Helicobacter pylori*, a germ that is likely to cause mucosal inflammation and peptic ulcers.

For the ulcer to heal permanently the germ must be destroyed. <Invented name> helps clear up or reduce infections caused by this germ. Your doctor may give you <Invented name> in combination with other medications to help destroy *Helicobacter pylori*.

2. What you need to know before you take <Invented name>

Do not take <Invented name>:
- if you are allergic to bismuth oxide or any of the other ingredients of this medicine (listed in section 6),
- if you have severe kidney problems (severe renal failure).

Warnings and precautions
Talk to your doctor or pharmacist before taking <Invented name>.

Do not use other bismuth containing medicines at the same time as <Invented name>.

Prolonged use of bismuth containing products is not recommended. Your doctor will usually not prescribe <Invented name> for more than two months.

Children and adolescents
<Invented name> is not intended for use in children and adolescents.

Other medicines and <Invented name>
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Do not take other medicines, especially those reducing gastric acidity half an hour before or after you take <Invented name>, as they may interfere with its effect.

<Invented name> may diminsh the effect of antibiotics called tetracyclines when used concomitantly.

<Invented name> with food and drink
Do not eat or drink anything half an hour before or after taking <Invented name>. Milk, fruit or fruit juce in particular can prevent the medicine from working properly.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking any medicine.

Do not take <Invented name> during pregnancy or if you are breast-feeding, unless if clearly necessary.

Driving and using machines
It is unlikely that <Invented name> will affect your ability to drive or use machines.

3. How to take <Invented name>

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The usual dose for adults and elderly is 4 tablets. They can be taken in the following ways:
- 1 tablet four times a day on an empty stomach, half an hour before each of three main meals and before bedtime

or
- 2 tablets twice daily, half an hour before breakfast and half an hour before dinner or before bedtime.

<Invented name> tablets should be swallowed whole with a sufficient amount of water.

Do not eat or drink half an hour before or after taking the tablet. If you skip a meal, you must still take the tablet(s).

Duration of treatment
For the treatment of duodenal or gastric ulcers the duration of one course of treatment is 4 to 8 weeks.

For the eradication of *H. pylori* the selection of combination therapy and duration of treatment (7 to 14 days) should consider the individual patient's drug tolerance, and should be undertaken in accordance with regional resistance patterns and treatment guidelines.

The maximum duration of one course of treatment is two months; do not take <Invented name> or other bismuth containing products for a period longer than that. Do not take any bismuth containing medicines in the two months following treatment with <Invented name>.

If you take more <Invented name> than you should
Do not worry if you have taken one or two additional tablets once. However, if you take many more tablets concurrently or within a short period of time, consult your doctor immediately. He/she will take appropriate measures to ensure bismuth is not absorbed. In addition, your kidney function will be monitored for several weeks.

If you forget to take <Invented name>
Do not take a double dose to make up for a forgotten one.

If you forget to take a dose, take it as soon as you remember, if it is not the time for the next dose to be administered. If this is the case, omit the forgotten dose.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Potentially life-threatening **allergic reaction** may occur while you are taking <Invented name>. Signs of allergy include sudden wheezing, swelling of your lips, tounge and throat, difficulties swallowing, rash or even fainting.
If you notice any of these symptoms, stop taking <Invented name> and contact a **doctor immediately.**
These effects are serious but very rare (may affect up to 1 in 10,000 people).

Other side effects include:

Very common (may affect more than 1 in 10 people):
- blackening of stools (faeces). This is nothing to worry about and will disappear soon after you stop treatment.

Uncommon (may affect up to 1 in 100 people):
- nausea, vomiting, constipation or diarrhoea;
- rash, pruritus.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store <Invented name>

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light and moisture.
This medicinal product does not require any special temperature storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

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6. Contents of the pack and other information

What <Invented name> contains
- The active substance is bismuth oxide. Each film-coated tablet contains 120 mg bismuth oxide (as tripotassium dicitratobismuthate (bismuth subcitrate)).
- The other ingredients (excipients) are maize starch, povidone K30, polacrillin potassium, macrogol 6000 and magnesium stearate (E470b) in the tablet core and polyvinyl alcohol, macrogol 4000, talc and titanium dioxide (E171) in the film coating.

What <Invented name> looks like and contents of the pack
Film-coated tablets (tablets) are white to almost white, round (diameter: 10 mm), film-coated, slightly biconvex with bevelled edges.

<Invented name> is available in packs containing 28, 30, 40, 42, 45, 56 and 60 film-coated tablets in blisters.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

This medicinal product is authorised in the Member States of the EEA under the following names:

[To be completed nationally]	

This leaflet was last revised in
[To be completed nationally]