SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Temol 10 mg/ml solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml solution for infusion contains 10 mg of paracetamol.

Each 100 ml vial contains 1000 mg of paracetamol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

Clear colorless to slightly yellowish, particle-free solution.

pH: 5.5
Osmolarity: 295 mOsm/L

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Short-term treatment of moderate pain, especially following surgery,
- Short-term treatment of fever,

when administration by intravenous route is clinically justified by an urgent need to treat pain or hyperthermia and/or when other routes of administration are not possible.

4.2 Posology and method of administration

Intravenous use.
The 100 ml vial is restricted to adults, adolescents and children weighing more than 33 kg.

Posology
Dosing based on patient weight (please see the dosing table here below)

Patient weight	**Dose per administration**	**Volume per administration**	**Maximum volume of Paracetamol (10 mg/ml) per administration based on upper weight limits of group (ml)****	**Maximum Daily Dose ***
> 33 kg to ≤ 50 kg	15 mg/kg	1.5 ml/kg	75 ml	60 mg/kg not exceeding 3 g

Patient weight	**Dose per administration**	**Volume per administration**	**Maximum volume of Paracetamol (10 mg/ml) per administration based on upper weight limits of group (ml)****	**Maximum Daily Dose ***
> 50 kg with additional risk factors for hepatotoxicity	1 g	100 ml	100 ml	3 g
> 50 kg and no additional risk factors for hepatotoxicity	1 g	100 ml	100 ml	4 g

***Maximum daily dose:** The maximum daily dose as presented in the table above is for patients that are not receiving other paracetamol containing products and should be adjusted accordingly taking such products into account.
****Patients weighing less will require smaller volumes.**

The minimum interval between each administration must be at least 4 hours. No more than 4 doses to be given in 24 hours.
The minimum interval between each administration in patients with severe renal insufficiency must be at least 6 hours.

Elderly
Dose adjustment is not required in elderly people (see section 5.2).

Severe renal insufficiency
It is recommended, when giving paracetamol to patients with severe renal impairment (creatinine clearance) (%

In adults with hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserves of hepatic glutathione), dehydration
The maximum daily dose must not exceed 3 g (see section 4.4).

Method of administration

Take care when prescribing and administering Paracetamol to avoid dosing errors due to confusion between milligram (mg) and milliliter (ml), which could result in accidental overdose and death. Take care to ensure the proper dose is communicated and dispensed. When writing prescriptions, include both the total dose in mg and the total dose in volume.

The paracetamol solution is administered as a 15-minute intravenous infusion.

To remove solution, use a 0.8 mm needle (21 gauge needle) and vertically perforate the stopper at the spot specifically indicated.

As for all solutions for infusion presented in glass vials, it should be remembered that close monitoring is needed notably at the end of the infusion, regardless of administration route. This monitoring at the end of the infusion applies particularly for central route infusion, in order to avoid air embolism.

For instruction on special precautions for disposal and other handling of the product, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance, to propacetamol hydrochloride (prodrug of paracetamol) or to any of the excipients listed in section 6.1.
- In cases of severe hepatocellular insufficiency.

4.4 Special warnings and precautions for use

Warnings

RISK OF MEDICATION ERRORS Take care to avoid dosing errors due to confusion between milligram (mg) and milliliter (ml), which could result in accidental overdose and death (see section 4.2).

It is recommended to use a suitable analgesic oral treatment as soon as this administration route is possible.

In order to avoid the risk of overdose, it should be checked that other medicines administered do not contain either paracetamol or propacetamol.

Doses higher than the recommended entail risk for very serious liver damage. Clinical symptoms and signs of liver damage (including fulminant hepatitis, hepatic failure, cholestatic hepatitis, cytolytic hepatitis) are usually first seen after two days of administration of the medicinal product with a peak seen usually after 4-6 days. Treatment with antidote should be given as soon as possible (see section 4.9).

Paracetamol can cause serious skin reactions. Patients should be informed of early signs of serious skin reactions. The use of paracetamol should be discontinued if signs of rash or other symptoms of hypersensitivity appear.

As for all solutions for infusion presented in glass vials, a close monitoring is needed notably at the end of the infusion (see section 4.2).

Precautions for use

Paracetamol should be used with caution in cases of:

- : syndrome
- severe renal insufficiency (creatinine clearance 30 ml/min) (see sections 4.2 and 5.2)
- chronic alcoholism
- low reserves of hepatic glutathione as a result of chronic malnutrition, anorexia, bulimia or cachexia
- dehydration
- glucose-6-phosphate dehydrogenase deficiency (may cause haemolytic anaemia).

This medicinal product contains less than 1 mmol sodium (23 mg) per 100 ml, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

- Probenecid causes an almost 2-fold reduction in clearance of paracetamol by inhibiting its conjugation with glucuronic acid. A reduction of the paracetamol dose should be considered for concomitant treatment with probenecid.
- Salicylamide may prolong the elimination half-life of paracetamol.
- Caution should be paid to the concomitant intake of enzyme-inducing substances including barbiturates, isoniazid, carbamazepine, rifampin, ethanol and others (see section 4.9)
- Concomitant use of paracetamol (4 g per day for at least 4 days) with oral anticoagulants may lead to slight variations of INR values. In this case, increased monitoring of INR values should be conducted

during the period of concomitant use as well as for 1 week after paracetamol treatment has been discontinued.

4.6 Fertility, pregnancy and lactation

Pregnancy
A large amount of data on pregnant women indicate neither malformative nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy, however, it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Breast-feeding
After oral administration, paracetamol is excreted into breast milk in small quantities. No undesirable effects on nursing infants have been reported. Consequently, Paracetamol may be used in breast- feeding women.

4.7 Effects on ability to drive and use machines

Paracetamol has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The following definitions apply to the incidence of the undesirable effects:
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<1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	Common	Rare	Very rare	Frequency not known
Blood and lymphatic system disorders			Thrombocytopenia, leucopenia, neutropenia	
Immune system disorders			Anapahylactic shock*, hypersensitivity reaction*	
Cardiac disorders				Tachycardia
Vascular disorders		Hypotension		
Hepatobiliary disorders		Hepatic transaminases increased		
Skin and subcutaneous tissue disorders			Serious skin reactions**, Rash*, Urticaria*	Erythema, pruritus, flushing
General disorders and administration site conditions	Reactions at injection site (pain and burning sensation)	Malaise		

* Very rare cases of hypersensitivity reactions such as anaphylactic shock, urticaria and skin rash have been reported and require discontinuation of treatment.
**Very rare cases of serious skin reactions have been reported (acute generalized exanthematous pustulosis, toxic epidermal necrolysis and Stevens-Johnson syndrome) and require discontinuation of treatment.

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 of the QRD template.

4.9 Overdose

There is a risk of liver injury (including fulminant hepatitis, hepatic failure, cholestatic hepatitis, cytolytic hepatitis), particularly in elderly people, in young children, in patients with liver disease, in cases of chronic alcoholism, in patients with chronic malnutrition and in patients receiving enzyme inducers. Overdosing may be fatal in these cases.

- Symptoms generally appear within the first 24 hours and comprise: nausea, vomiting, anorexia, pallor and abdominal pain.

  Overdose (7.5 g or more of paracetamol in a single administration in adults or 140 mg/kg of body weight in a single administration in children) causes hepatic cytolysis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy which may lead to coma and death. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with decreased prothrombin levels that may appear 12 to 48 hours after administration. Clinical symptoms of liver damage are usually evident initially after two days, and reach a maximum after 4 to 6 days.

Emergency measures

- Immediate hospitalisation
- Before beginning treatment, take a tube of blood for plasma paracetamol assay, as soon as possible after the overdose.
- The treatment includes administration of the antidote, N-acetylcysteine (NAC) by the i.v. or oral route, if possible before the 10^{th} hour. NAC can, however, give some degree protection even after 10 hours, but in these cases prolonged treatment is given.
- Symptomatic treatment
- Hepatic tests must be carried out at the beginning of treatment and repeated every 24 hours. In most cases hepatic transaminases return to normal in one to two weeks with full restitution of liver function. In very severe cases, however, liver transplantation may be necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, other analgesics and antipyretics, ATC code: N02BE01

The precise mechanism of the analgesic and antipyretic properties of paracetamol has yet to be established; it may involve central and peripheral actions.

Paracetamol provides onset of pain relief within 5 to 10 minutes after the start of administration. The peak analgesic effect is obtained in 1 hour and the duration of this effect is usually 4 to 6 hours.

Paracetamol reduces fever within 30 minutes after the start of administration with a duration of the antipyretic effect of at least 6 hours.

5.2 Pharmacokinetic properties

Adults

Absorption

Paracetamol pharmacokinetics is linear up to 2 g after single administration and after repeated administration during 24 hours.

The bioavailability of paracetamol following infusion of 500 mg and 1 g is similar to that observed following infusion of 1 g and 2 g propacetamol (corresponding to 500 mg and 1 g paracetamol respectively). The maximal plasma concentration (C_{max}) of paracetamol observed at the end of 15-minutes intravenous infusion ((

Distribution

The volume of distribution of paracetamol is approximately 1 l/kg.

Paracetamol is not extensively bound to plasma proteins.

Following infusion of 1 g paracetamol, significant concentrations of paracetamol (about 1.5 µg/ml) were observed in the cerebrospinal fluid as and from the 20th minute following infusion.

Biotransformation

Paracetamol is metabolised mainly in the liver following two major hepatic pathways: glucuronic acid conjugation and sulphuric acid conjugation. The latter route is rapidly saturable at doses that exceed the therapeutic doses. A small fraction (less than 4%) is metabolised by cytochrome P450 to a reactive intermediate (N-acetyl benzoquinone imine) which, under normal conditions of use, is rapidly detoxified by reduced glutathione and eliminated in the urine after conjugation with cysteine and mercapturic acid. However, during massive overdosing, the quantity of this toxic metabolite is increased.

Elimination

The metabolites of paracetamol are mainly excreted in the urine. 90% of the dose administered is excreted in 24 hours, mainly as glucuronide (60-80%) and sulphate (20-30%) conjugates. Less than 5% is eliminated unchanged. Plasma half-life is 2.7 hours and total body clearance is 18 l/h.

Special populations

Renal insufficiency

In cases of severe renal impairment (creatinine clearance 10-30 ml/min), the elimination of paracetamol is slightly delayed, the elimination half-life ranging from 2 to 5.3 hours. For the glucuronide and sulphate conjugates, the elimination rate is 3 times slower in subjects with severe renal impairment than in healthy subjects. Therefore, it is recommended, when giving paracetamol to patients with severe renal impairment

tration to 6 hours

(see section 4.2).

Elderly

The pharmacokinetics and the metabolism of paracetamol are not modified in elderly people. No dose adjustment is required in this population.

Paediatric population

The pharmacokinetic parameters of paracetamol observed in infants and children are similar to those observed in adults, except for the plasma half-life that is slightly shorter (1.5 to 2 hours) than in adults. In neonates, the plasma half-life is longer than in infants i.e. around 3.5 hours.
Neonates, infants and children up to 10 years excrete significantly less glucuronide and more sulphate conjugates than adults.

Table: Age related pharmacokinetic values (standardised clearance, *CL_{std}/F_{oral} ($l.h^{-1}$ 70 kg^{-1})

Age	Weight (kg)	CL_{std}/F_{oral} ($l.h^{-1}$ 70 kg^{-1})
40 weeks PCA	3.3	5.9
3 months PNA	6	8.8
6 months PNA	7.5	11.1
1 year PNA	10	13.6
2 years PNA	12	15.6
5 years PNA	20	16.3
8 years PNA	25	16.3

*CL_{std} is the population estimate for CL
PCA: postconceptional age
PNA: postnatal age

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans beyond the information included in other sections of the SmPC.

Studies on local tolerance of paracetamol in rats and rabbits showed good tolerability. Absence of delayed contact hypersensitivity has been tested in guinea pigs.

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cysteine hydrochloride monohydrate
Disodium phosphate dihydrate
Hydrochloric acid (for pH-adjustment)
Mannitol
Sodium hydroxide (for pH-adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

24 months

Shelf life after first opening of the vial:
Use immediately after opening.

6.4 Special precautions for storage

Do not refrigerate or freeze.
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The solution for infusion is packed in a 100 ml colourless type II glass vial, closed with a bromobutyl rubber stopper and sealed with an aluminium flip-off cap, and inserted in the carton.

Pack sizes:
1 vial, 10 (10 x 1) vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before administration, the product should be visually inspected for any particulate matter and discoloration.
For single use only.
Any unused solution should be discarded.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sandoz GmbH, Kundl Biochemiestrasse 10, A-6250 Austria 10, A-6250 AUSTRIA

8. MARKETING AUTHORISATION NUMBER(S)

Not applicable

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not applicable

10. DATE OF REVISION OF THE TEXT

August 2020