الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Guidance for Paracetamol-Containing Oral Liquid Dosage Forms Products Intended for Pediatrics

Version 1.0

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Saudi Food & Drug Authority

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Saudi Food and Drug Authority

Vision and Mission

Vision

To be a leading international science-based regulator to protect and promote public health

Mission

Protecting the community through regulations and effective controls to ensure the safety of food, drugs, medical devices, cosmetics, pesticides and feed

Document Control

Version	Author	Date	Comments
First Draft	Executive Directorate of Pharmacovigilance	29 January 2020	-
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Implementation Notice

Final version of this document is effective immediately for all new products seeking marketing authorization.

For registered products, companies encouraged to submit variation application to implement the requirement of the guideline.

After 18 months of publishing the final version of this document, the implementation is mandatory for all registered products.

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1. INTRODUCTION

1.1. Objective

The Drug Sector in Saudi Food & Drug Authority (SFDA) has developed this document to promote safer use of products containing paracetamol in pediatric under 12 years old by minimizing the potential of paracetamol overdosing and toxicity due to medication errors or accidental ingestion.

1.2. Background

Paracetamol is one of the most frequently administered medications to pediatrics worldwide. The current dosing instructions of registered paracetamol label mostly based on age not weight, which are imprecise and may result in inaccurate dosing due to marked variations in the weight of children of the same age. In 2015, a committee of experts led by SFDA has met to review the appropriate dosage labeling of paracetamol in children and infants.

The SFDA committee concluded a number of recommendations including:

1. Due to the availability of different doses for the same child's age/weight, corrective action should be taken for paracetamol dosage labeling, based on the child's weight to avoid sub-therapeutic dosing.
2. Ensuring the availability of a precise measuring device packaged within all marketed products.
3. Investigate dosage labeling for all paracetamol products available in the market.

1.3. Scope

To provide applicants with guidance on the requirements necessary to receive marketing authorization for over the counter (OTC) oral liquid dosage forms containing paracetamol apply to both single-ingredient and combination-ingredient products for pediatric under 12 years of age.

1.4. Related Guidelines

This document should be read in conjunction with the following documents:

- The GCC Guidance for presenting the SPC, PIL and Labeling Information.
- Guidance for Graphic Design of Medication Packaging.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

In Saudi Arabia, paracetamol is available in several dosage forms and concentrations including:

2.1.Strengths

- Paracetamol 120mg/5mL
- Paracetamol 125mg/5mL
- Paracetamol 160mg/5mL
- Paracetamol 100mg/mL

2.2.Pharmaceutical Forms

Oral liquid formulation such as solutions, suspensions, syrup, drops and elixir.

3. REQUIREMENTS

3.1.Patient Information Leaflet (PIL)

In addition to the GCC Guidance for presenting the SPC, PIL and Labeling Information and the guidance for Graphic Design of Medication Packaging, the following are special considerations for products containing paracetamol as OTC products:

3.1.1. Therapeutic Indications

To relieve mild to moderate pain and to reduce fever in many conditions including headache, toothache, teething, feverishness, colds, influenza, and following vaccination.

3.1.2. Dosage Direction for Children Under 12 Years

The dose should be weight-related dosing in the label instructions. If the weight of the child is unknown, age-related dosing is provided (See tables 1 and 2).

Table 1: Dosage for children under 12 years of age: 25 mg/mL; 24 mg/mL; 32 mg/mL paracetamol

Age (Years)	Body weight (kg)	Maximum Single dose				Maximum daily dose			
		mg	25 mg/ mL	24 mg/ mL	32 mg/ mL	mg	25 mg/ mL	24 mg/ mL	32 mg/ mL
2-3	11.0-15.9	160	6.4 mL	6.6 mL	5 mL	800	32 mL	33.3 mL	25 mL
4-5	16.0-21.9	240	9.6 mL	10 mL	7.5 mL	1200	48 mL	50 mL	37.5 mL
6-8	22.0-26.9	320	12.8 mL	13.3 mL	10 mL	1600	64 mL	66.6 mL	50 mL
9-10	27.0-31.9	400	16 mL	16.6 mL	12.5 mL	2000	80 mL	83.3 mL	62.5 mL
11 to under 12	32.0-43.9	480	19.2 mL	20 mL	15 mL	2400	96 mL	100 mL	75 mL
Age (months)	**Body weight (kg)**	**Maximum Single dose**				**Maximum daily dose**			
		mg	25 mg/mL	24 mg/mL	32 mg/mL	mg	25 mg/mL	24 mg/mL	32 mg/mL
0-1	2.7-3.9	40	1.6 mL	1.6 mL	1.25 mL	200	8 mL	8.3 mL	6.25 mL
2-3	4-5.4	60	2.4 mL	2.5 mL	1.8 mL	300	12 mL	12.5 mL	9.3 mL
4-11	5.5-7.9	80	3.2 mL	3.3 mL	2.5 mL	400	16 mL	16.6 mL	12.5 mL
12-23	8.0-10.9	120	4.8 mL	5 mL	3.75 mL	600	24 mL	25 mL	18.75 mL

To minimize dosing errors, paracetamol oral drops solution of 100 mg/mL concentration should not be concurrently labeled for both infants (under 2 years) and children (of 2 years and older). Thus, a clear statement of "this product for infants under 2 years" should be available.

Table 2: Dosage of children under 2 years,: 100 mg/mL Paracetamol oral drops

Age (Months)	Body weight (kg)	Maximum Single dose		Maximum daily dose	
		mg	100 mg/mL	mg	100 mg/mL
0-1	2.7-3.9	40	0.4 mL	200	2 mL
2-3	4-5.4	60	0.6 mL	300	3 mL
4-11	5.5-7.9	80	0.8 mL	400	4 mL
12-23	8.0-10.9	120	1.2 mL	600	6 mL

3.1.3. Special considerations

The patient information leaflet should include the following:

- The recommended single dose and maximum daily dose in **mL**, as well as the dosing interval for the product. The maximum daily dose may be expressed as: "Do not take more than x mL or x doses in 24 hours".
- "Seek medical advice before giving to the preterm neonate or term neonates <10 days".
- "Repeat 4 – 6 hourly up to 5 times per day if required. No more than 5 doses in any 24-hour period, unless directed by physician".
- For **25 mg/mL; 24 mg/mL; 32 mg/mL**: "Should not be used for more than 5 days for children ≥2 years and 3 days for infants (<2 years) except on medical advice."
- For **100mg/mL**: "Should not be used for more than 3 days at a time except on medical advice."
- "Should not be used with other paracetamol-containing products."
- Instructions specific for oral liquid dosage form, i.e. should not include all dosage forms of paracetamol in one PIL such as (tablet or suppositories,).

3.1.4. Warnings

- Under section 2 "Before you take or use the product": Liver warning: (should be bold font type): "This product contains paracetamol. Maximum daily dose is (XX mL) in 24 hours. Severe or possibly fatal liver damage may occur if you take more than the recommended dose in 24 hours or with other drugs containing paracetamol."
- "DO NOT USE with other drugs containing paracetamol. If you are not sure whether a drug contains paracetamol, ask a doctor or pharmacist."
- Do not use if you are allergic to paracetamol or any other ingredient in this product

3.2. Outer and Immediate Packaging

In addition to The GCC Guidance for Presenting the SPC, PIL, and Labeling Information, and SFDA Guidance for Graphic Design of Medication Packaging, the following are special considerations for products containing paracetamol as OTC Products:

- The quantitative declaration of the medicinal ingredients (paracetamol) on any panel of the immediate and outer packaging should be prominently displayed and should be further

identified by the therapeutic class or indication “paracetamol (analgesic/antipyretic) 32 mg/mL”.

- Concentration of paracetamol should appear in bold font type, clear font size and in black text with a white background in the middle of the label.
- It is recommended that the age group for which the medicine is intended should be stated on the outer packaging.
- If there is an image of a child on the outer packaging, the image should be representative of the age range for which the product is suitable.

The immediate and outer packaging should contain the below warnings:

- DO NOT USE with other drugs containing paracetamol. If you are not sure whether a drug contains paracetamol, ask a doctor or pharmacist.
- DO NOT USE if you are allergic to paracetamol or any other ingredient in this product
- For oral suspensions, shake the bottle well before use.

3.3.Pack Size and Container

Packaging should be standard child-resistant to prevent or delay pediatrics from opening bottles, giving caregivers reasonable time to intervene.

3.4.Combination

Marketing authorization holders should apply outside of the labeling standard if they wish to combine paracetamol with medicinal ingredient(s) such as a sedative, antitussive, antihistamine. Please note that all labeling requirements for paracetamol are also applied to products combining paracetamol with any other medicinal ingredient.

The statement: “this product Contains paracetamol and other Ingredients” should appear in bold font type and clear font size in the top right corner of the label. In addition, the text for “this product contains paracetamol” should appear in red with a white background.

- For small package sized products: Consideration will be given for products with small package sizes. However, the text for “Contains paracetamol” should appear prominently in bold font type in red with a white background in the top right corner of the label.

3.5.Delivery Device

- For oral liquid formulations, it is required that an appropriate dosage delivery device be provided, such as a calibrated and labeled oral syringe or dosing cup.
- As the dosing directions should be in milliliters (mL), accordingly the dosage delivery devices should have calibrated units of liquid measurement expressed in milliliters (mL) only.
- The following statement should be included with the directions for use: “Use only the measuring device provided”, and include instructions that are consistent with the measuring device.

REFERENCES:

1. Health Canada Revised Guidance Document: Acetaminophen Labelling Standard. September 2016.
2. US Food and Drug Administration. Over-the-Counter Pediatric Oral Liquid Drug Products Containing Acetaminophen: Guidance for Industry. August 2015.